CLINICAL MANAGEMENT OF MALARIA

TRAINING MATERIAL AND MODULAR EXERCISES

NATIONAL ANTI MALARIA PROGRAMME

(Enhanced Malaria Control Project)

Directorate General of Health Services

Ministry of Health and Family Welfare

22, Sham Nath Marg, Delhi-110054

Govt. of India

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PREFACE

Early Diagnosis and Prompt Treatment (EDPT) of malaria cases constitutes, interalia, the main strategy for malaria control. Appropriate treatment of cases will reduce sickness duration, complications and mortality. In addition the administration of gametocidal drug like Primaquine will make the patient incapable of transmitting the disease. Parasite control by EDPT would be operationally feasible and cost-effective as compared to vector control.

The clinical presentation of malaria cases have undergone considerable change during the recent past. Increase in proportion of *P. falciparum* cases, drug resistance, frequent movement of population, increase in epidemic potential, have all contributed to the increase in number of severe and complicated malaria cases, thereby increasing mortality rate. While treatment of uncomplicated malaria is simple where as severe and complicated cases need specialised management. It is, in this context, a referral system needs to be developed further so that such serious cases have an early access to proper treatment.

Efforts have been made to provide training material and case studies in this module. The trainers may use the module in part or as whole according to the target groups involved. In some batches the trainers may like to expose the participants to the other public health aspects of malaria control for which separate notes/documents are available.

I am confident that this module will help the clinicians and the trainers in the proper management of malaria cases and help to reduce the mortality and morbidity as a whole.

Suggestions to improve the material will be welcomed and may be sent to the Directorate of NAMP.

Delhi
March, 1998

SHIV LAL

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SECTION-I

CHEMOTHERAPY—ANTIMALARIALS

Introduction

During the present century, there has been an extensive research on chemotherapy of malaria and as a result a large number of antimalarials have been developed. After screening thousands of chemical compounds for their antimalarial properties, safe and potent antimalarials were selected and marketed for treatment of patients suffering from malaria.

In retrospect, looking at the specific treatment of malaria infections, Quinghaosu is the oldest herbal preparation. Nearly a thousand years ago it was used in China for treating intermittent fevers.

Later on, Quinine was used all over the world as a chemotherapeutic agent for treatment of malaria. Even now, it is still the drug of choice for treatment of complicated *P.Falciparum* infections. In 1638, Anna del Chinchon, wife of viceroy of Peru, was cured of a fever episode most probably due to malaria, by an extract from the bark of a tree which was being used by local tribals as a cure for fever in Peru. There is a romantic anecdote which tells how the name of Lady Cinchon was misspelt as 'Chinchona' and the tree was named after her because of the specific cure achieved in her case.

The cinchona bark was introduced in Europe around the year 1643. Since then, it has been extensively used for treatment of intermittent fevers and has been recognised as a specific remedy for these fevers. Later on, after the discovery of malaria parasite, it was found to have action on all species of Plasmodium. In 1820, active alkaloid of Quinine was isolated from cinchona and was found to be superior in treatment of malaria cases as compared to cinchona decoction Totaquina. For nearly three centuries Quinine was the only chemotherapeutic agent available for specific treatment against malaria parasite infections. The cinchona tree was brought by Portuguese and plantations were established in Jawa, India and parts of Africa. Nearly 90% of the supplies of Quinine came from these plantations. During world war I and II the supplies from these plantations were cut off from one of the warring groups and under field conditions, all troops were exposed to high risk of malaria. It was observed that more often than not, an outcome of the battle was decided by the disability due to malaria rather than the lack of weaponry. This situation generated intense interest in developing synthetic antimalarials. Thus it is apparent that just as malaria has historically shaped the outcome of the world wars, so also these wars have determined the approach to malaria chemotherapy.

Acridine dyes were found to have some effect on malaria parasite. After testing many chemical compounds of this group i.e. 9-Aminoacridines, Mepacrine was thought to be superior to Quinine in its action against malaria parasite. Prolonged chemoprophylaxis with Quinine produced many adverse effects, some of them were quite serious and disability was sometimes permanent. Tinnitus, deafness, dizziness, ocular and cardiac symptoms were some of the worst side effects. Due to these serious and debilitating side effects, drug compliance by the patients was poor both during chemoprophylaxis and treatment of acute episodes of malaria. On the other hand, it was found that Mepacrine produced comparatively milder side effects. Since the drug was deposited in the skin and gave a strange yellow colour to the skin of soldiers, it was not very popular with persons put on chemo-prophylaxis. The adverse reactions of Mepacrine were mostly gastro-intestinal disorders, skin discolouration and skin eruptions.

Due to adverse reactions of Mepacrine, further research was continued and as a result Biguanide group of drugs became available in 1944. They were found to be less toxic but equally effective in the control of malaria infection. However, when Poludrine was used for chemoprophylaxis over a long period specially among the troops and tea garden labourers of India, there were reports of drug resistance within a short period of time. Diaminopyrimidines were also synthesised during the same period and were found to have adequate antiparasitic action but this group showed greater adverse reactions when used as a long-term prophylactic/suppressive agent. 4-aminoquinolines were synthesised much earlier than any of these drugs but were put on the shelf due to misconception that antimalarial activity of this group of compounds was much lower than that of 8-aminoquinolines and Mepacrine. One of the 8-aminoquinolines to be synthesised in 1920 was Primaquine. This drug was also not brought in general use till 1952, earlier when it was used as a schizonticidal drug, its action on asexual erythrocytic stages of malaria parasite was found to be slow and the high chemotherapeutic doses administered for schizonticidal agent was stopped. During the intervening period gametocidal effect was observed and since then it is being exclusively used as an anti-relapse and gametocidal drug for radical cure in malaria infection.

The Sulfonamide like sulfadiazine was available in 1930. Later on in 1950s, the long acting sulpha group of drugs were introduced. Large number of antibiotics were tested and a few of them were found to have specific action on malaria parasite but in the therapeutic doses recommended and tolerated, their action was found to be slow. Treatment with antibiotics has to be continued for a longer period i.e. 7 to 10 days as compared to single day or three days regimen of chloroquine.

Chloroquine remained supreme in the treatment of acute malaria episodes because of its fast action on parasites and antipyretic property which produces quick remission of fever and parasitaemia.

The review of the research on development of antimalarials showed that search for new antimalarials did not have the same urgency as was felt during world wars I and II, mostly due to the fact that safe and fast acting antimalarials like chloroquine and Amodiaquine

were available. The properties of these compounds were reassuring and the need for further research was not felt very urgent, more so because the resistance to these drugs in human parasite did not develop quickly and experts believed that like Quinine the resistance to these drugs would not develop soon. However, resistance to chloroquine in p. falciparum was recorded in two widely apart epicentres in Latin America in 1960 and along Thai-Kampuchia border during 1962. Nearly simultaneous emergence of resistance to chloroquine in p. falciparum in two different ecosystems instilled a sense of urgency for developing newer antimalarials. Thereafter, several chemical compounds were tested for their antimalarial activity and new combinations like long acting sulpha group of drugs with pyrimidines (a combination which is extensively used since 1950), Dapsone, Mefloquine and Halofantrine have been found to be effective. These drugs are very effective for the treatment of chloroquine resistant p. falciparum strain. Long acting sulpha group of drugs alone have very little and slow action on malaria parasite. Their action is potentiated in combination with Diaminopyrimidines. After 1950, their use as a second line of treatment in *P. falciparum* malaria infections resistant to chloroquine was recognised.

However, most of the synthetic antimalarials marketed for treatment of chloroquine resistant p. falciparum infections do select out resistant strains of p. falciparum such strains also show cross resistance to compounds of related groups. Thus there is a sense of greater urgency to develop new antimalarial compounds as well as to rationalise the use of existing antimalarials. Development of a new compound, its testing and ultimate marketing take a long time, the period may extend as long as 8 to 10 years or more. Therefore, malariologists all over the world are worried and they are trying to rationalise the chemotherapeutic approach to malaria cases.

In the meanwhile chinese scientists started looking at their traditional medicines used for treatment of malaria so as to develop alternative drugs for treatment of chloroquine resistant p. falciparum. They isolated active ingredients from their traditional herb Quinghaosu and drugs like Artemesinine, Artemether and Artesunate were tested for their efficacy against malaria parasites. These compounds are highly active against asexual erythrocytic stages of all species of human malaria parasites. It has been found that they are safer than Quinine or chloroquine but have no action on sexual stages or tissue phase of malaria parasite in human beings. The major drawback is that a large number of breakthroughs occur in p. falciparum cases treated with Quinghaosu derivatives.

As the primary objective of malaria chemotherapy is to provide prompt clinical and parasitological relief to the persons suffering from malaria, most of the antimalarials are evaluated and utilised on the basis of their action against asexual erythrocytic forms of malaria parasite because these stages of parasites are responsible for the clinical attack. On the other hand, some drugs have poor/slow schizonticidal action but are essential for the treatment of malaria infection on account of their specific action against 'hypnozoites' and 'gametocytes'.

Most of the antimalarials can be classified either according to their effect on different stages of malaria parasite or on the basis of their chemical nature. The list of antimalarials according to the chemical groups is given in Table - 3.1 :—

Table - 3.1 :

Antimalarial Drug	Chemical Groups
CINCHONA ALKALOIDS	DIAMINOPYRIMIDINES
Quinine	Pyrimethamine
Quinidine	Trimethoprim
9-AMINOACRIDINES	8-AMINOQUINOLINES
Mepacrine	Primaquine
	Pamaquine
	Quinocide
BIGUANIDES	
Proguanil	
Chlorproguanil	
4-AMINOQUINOLINES	
Chloroquine	
Amodiaquine	
SULFONES	
DAPSONE	
SULFONAMIDES	
Sulfadimethoxine	
Sulfamethoxypyridazine (Sulfalene)	
Sulfadoxine	
ANTIBIOTICS	
Tetracycline — Norfloxacin	
Doxycylice — Ciprofloxacin	
Minocycline — Ofloxacin	
Clindamycin	
NEW COMPOUNDS	
Mefloquine	
Halofantrine	
Quinghaosu and its derivatives,	
Artemisinin — Artemether	
Artesunate — Arteether	

Action of Antimalarials on Different Stages of Plasmodium

It is essential to understand the classification of antimalarials on the basis of their action on different stages of malaria parasite because this property of an antimalarial compound helps in formulating a rational chemotherapeutic approach towards treatment of malaria.

The malaria infection in human being starts with the introduction of sporozoites in the human body from an infective mosquito bite. Some of the sporozoites are killed by phagocytosis but a large number of them manage to survive. They enter the liver cells—the 'hepatocytes' and undergo further development. The sporozoites remain in blood circulation for a period of nearly half an hour. During this period of their free circulation in the human body, the sporozoites are metabolically dormant. Probably due to this reason, none of the antimalarials are picked up by them and these chemical agents have no action on sporozoites while they are freely circulating in blood. Drugs which prevent establishment of infection in a human being are called true *casual prophylactic.* There is no true casual prophylactic antimalarial for malaria infection so far.

The sporozoites after entry into hepatocytes develop as tissue schizonts. Some of the sporozoites go into the dormant stage called 'hypnozoites'. They remain dormant in the hepatocytes for varying periods of time depending on the strain characteristics of p. vivax or p. ovale. During the tissue phase i.e. primary tissue phase and hypnozoite stage, some of the antimalarials show adequate activity. These drugs belong to Biguanide, Pyrimidine and 8-Aminoquinoline series. Out of these groups, only 8-Aminoquinolines show profound action against hypnozoites.

After a period of development and multiplication of parasites in hepatocytes, the merozoites are released in the blood stream. They infect the circulating RBCs. The erythrocytic stages of malaria parasite i.e. the various stages of the erythrocytic schizogony are affected by antimalarial compounds belonging to Quinoline, 4-Aminoquinolines groups, Sulfonamides in combination with Pyrimidines, Antibiotics, Mefloquine and derivatives of Quinghaosu.

These group of drugs have very little action on sexual stages of erythrocytic cycle of malaria parasite. Only 9-Aminoquinolines have action on mature gametocytes. It has been inferred that 4-Aminoquinolines have action on developing stages of gametocytes and the presumption seem to be valid because chloroquine acts during the developmental stages of parasites by interfering with the utilisation of haemoglobin by the parasite thus actively interfering with the metabolism of the parasite. Therefore, it can be postulated that those stages of malaria parasite will be affected by chloroquine which are metabolically active. The metabolically dormant stages like sporozoites, mature gametocytes, hypnozoites, free circulating merozoites and mature schizonts will not respond to conventional antimalarials. Classification of antimalarials on the basis of their action on different stages of malaria parasite in human body is given in the Table - 3.2.

Table - 3.2 : **Classification of antimalarials on the basis of their action on different stages of malaria parasite**

SPOROZOITES	TISSUE PHASE		ERYTHROCYTIC STAGES	
	PRIMARY TISSUE PHASE	PERSISTENT TISSUE PHASE HYPNOZOI-TES	SCHIZOGONY RING TROPHOZOI-TES SCHIZONT	SEXUAL STAGES
No drug available	BIGUANIDES - Proguanil Paludrine (in *Pf*) - Cholorproquanil - PYRIMIDINES - Trimethoprim - (in *Pf*)	8-AMINO QUINOLINES - Primaquine	QUINOLINES - Quinine	8-AMINO-QUINO-LINES - Primaquine
	8-AMINO-QUINOLINES - Primaquine (Both in *Pv* & *Pf*)		4-AMINO-QUINOLINES - Chloroquine - Amodiaquine	*4-AMINO-QUINO-LINES - Chloroquine
			** SULFONA-MIDES - Sulfalene - sulfame-thaxazole	OTHERS @ - Pyrime-thamene @ Proguanil
			ANTIBIOTICS - Tetracycline - Doxycycline	
			OTHERS - Mefloquine - Quinghaosu and its deriva-tives -Artemisinin -artemether -Artesunate -Arteether -halofantrine	
True Casual Prophylactic	Casual Prophylactic	Anti-relapse (Radical Cure)	Schizonticidal (also used as suppressant)	Gametocy-tocidal

@Sprontocidal (in *Pv* & *Pf*)

*action against gametocytes of p. vivax, also active against developing gametocytes of *P.falciparum*.

**this group has very little or negligible action on asexual stages of *P. vivax*.

Action of long acting sulphanamides is potentiated in combination with :--
- Pyrimethamine
- Trimethoprim
- in proportion of 20:1 and 8:1 respectively

2. DETERMINANTS OF ANTIMALARIAL DRUG EFFICACY

The efficacy of an antimalarial drug depends on:-

- Rate of absorption on oral administration
- Time taken to achieve therapeutic levels of drug concentration in blood
- Duration of chemotherapeutically effective blood concentration
- Their storage in body tissues
- Their ability to bind with proteins, especially plasma proteins
- Their rate of conversion into metabolites
- Their rate of excretion
- Their preferential concentration in infected RBCs

Their action on different metabolic systems of malaria parasite:— They may act as anti-metabolic agents thereby interfering with supply, or use by the parasite of nutrient Amino acids/enzymes, or they may have action on RNA/DNA affecting its replication or other functions. Thus these antimalarial drugs destroy the parasites by interfering with their development or multiplication. Some of the antimalarial drugs act as anti-metabolic compounds by interfering with dihydrofolate reductase (DHFR) inhibitors such as Pyrimethamine.

- Toxicity to human beings:— Some drugs are more toxic to people having certain genetic abnormalities notably G6PD deficiency. The genetically defective red blood cells are more readily haemolised by 8-Aminoquinolines such as Primaquine.

- Efficacy of drug:— For reasons not well known, some drugs are more effective against one species of parasite than the others, in this group are sulfones and sulfonamides. They act against *P. falciparum* but have very little action on other species of malaria parasite.

2.1 Mechanism of Antimalarial activity of the four groups of compounds is discussed below:-

The first group consists of Quinine and related group of compounds which includes chloroquine, Amodiaquine, Quinine and mefloquine. These drugs act as very effective schizonticidal agents. In case of chloroquine, it has been observed that the drug concentration is 7 to 8 times more in RBCs than in plasma. It is much more in those RBCs which are parasitised. In case of resistant strain, the concentration in parasitised RBCs is lower than what is observed in non-resistant strain infection. One of the hypotheses is that there is an active efflux of drug from RBCs, infected with resistant strain. The drug interferes with haemoglobin digestion preventing parasite from using the required nutrients. The drug gets concentrated in parasite acid vehicle, raises intracellular PH and thus inhibition of acid proteases occurs. The resulting alkaline environment is disruptive. The drug acts on RNA and DNA of the parasite. The aminoacids essential for parasite growth are blocked by this drug.

Quinine acts by similar mechanism and also indirectly by producing lysis of parasitised red blood cells. This lysis of red blood cells results in casting out the immature parasites which are subsequently destroyed by defence mechanism of the host.

The second group includes sulfones and sulphonamides which act as PABA inhibitors. These drugs act as anti-metabolites preventing the parasite from making dihydrofolate, an essential enzyme for its nuclear division. The parasite may survive the action of the drug if it has the capacity to utilise an alternative enzyme system.

The third group of drugs which are DHFR inhibitors includes Pyrimethamine, Proguanil and Trimethoprim. These anti-metabolites have high affinity for the enzyme dihydrofolate reductase. These drugs remove the reductase thereby interfering with nuclear division of the parasite.

The fourth group of drugs having action on parasite Membrane Disruptors i.e., anti-nuclear, includes the traditional Chinese herbal preparation - Quinghaosu (Artemisinin, from the herb *artemisia annua* and its derivatives - Artemether and Artesunate) which act through their anti-sesquiterpene peroxide structure and generation of free radicals. Damage occurs to parasite nuclear and cellular membranes, mitochondria and food vacuole; autophagic vacuoles then appear and the parasite disintegrates. The destructive action is more rapid than that of chloroquine or Quinine.

2.2. PHYSICIAN'S OPTION

Out of a large number of antimalarial compounds available for treatment of malaria, the physician while treating a malaria case has to decide the drug of choice and the options available are decided on the basis of :—

(i) The route of administration - oral, intramuscular or intravenous,

(ii) Rapidity of absorption from the route of administration,

(iii) Time taken to attain therapeutically effective blood concentration,

(iv) Half life of the drug,

(v) Excretion time/rate,

(vi) Adverse reactions such as idiosyncrasy, chronic toxicity on prolonged use,

(vii) Contraindications and Precautions to be observed as well as the efficacy of antidotes available for treatment of acute or chronic toxicity.

(viii) Nursing care required/available if adverse reactions are encountered.

2.3. GENERAL RULES OF ANTIMALARIAL THERAPY

Before the details regarding the mode of action, dosage etc. of different antimalarials are discussed, it is necessary to lay down some ground rules for use of antimalarials. These rules will help the physician in choosing appropriate treatment schedule for a patient suffering from malaria.

(i) Oral administration of antimalarial should be preferred in all cases who can swallow and retain antimalarial compounds, as most antimalarials are absorbed rapidly.

(ii) Intravenous antimalarials like Quinine or Artemisinin should be used in comatosed patients or patients who cannot retain and vomit out antimalarials administered orally due to gastro-intestinal irritation.

(iii) An antimalarial with good chemotherapeutic index (difference between clinically effective and toxic dosage) should be chosen for oral and parentral administration.

(iv) Chloroquine is the drug of choice for treatment of infections with *P. vivax*, *P. malariae* and *P. falciparum* malaria parasites.

(v) Only in cases where infection with *P. falciparum* strain resistant to chloroquine is suspected, other antimalarials could be tried.

(vi) In ambulatory cases of *P. falciparum* resistant strain without complications, long acting sulpha-pyrimethamine combination is the drug of choice.

(vii) In severe and complicated malaria cases, intravenous Quinine should be administered. Internationally accepted dosage should be strictly adhered to, so that future complications and toxic manifestations are avoided.

(viii) While administering the intravenous Quinine, patients should be carefully monitored for hypoglycaemic crisis and cardio-vascular complications. The arrangements should be made for appropriate investigations and suitable supportive treatment.

3. PROPERTIES AND USE OF ANTIMALARIAL COMPOUNDS
CINCHONA ALKALOIDS

Quinine or Quinidine are cinchona derivatives. At present their synthesis is expensive and commercially not feasible. Quinidine can be used as an alternative if quinine is not available. Cardiac side effects are more common. Quinidine therefore strict cardiac monitoring is essential with this drug.

3.1 QUININE

(i) Formulations marketed

Quinine is available as dihydrochloride salt for intramuscular or intravenous injections. Each ampule of 2 cc contains 600 mg of Quinine salt i.e. 300 mg per cc.

Three salts of Quinine are marketed for oral administration i.e. sulphate, hydrochloride and dihydrochloride as tablets, each tablet contains 300 mg of Quinine salt.

(ii) Dosage

(a) Oral administration

Adult Dose

600 mg Quinine salt three times a day for seven days (10 mg Quinine salt per kg body weight 8 hourly for seven days).

Children can tolerate higher dose of Quinine i.e. 10 mg per kg body weight for subsequent three days.

(b) Intramuscular Injection

10 mg per kg/body weight at 8 hourly intervals. Quinine preparation is adequatley diluted with normal saline. If intramuscular injection is unavoidable, it should be given deep intramuscularly. If after dilution, the quantity of injectable solution is more, it should be distributed at multiple sites.

Intramuscular Quinine injection should be given very carefully in gluteal muscles ensuring that injected fluid does not lie near the arterial or neural plexus, as it may lead to arterial spasm resulting in necrosis and gangrene in the area of its supply. Subsequent fibrosis may lead to paralysis of the limb/muscle supplied by the nerve enmeshed in fibrosis. As most of the patients of malaria suffer from malnutrition and muscles are emaciated, it is not advisable to give intramuscular injection. If unavoidable it should be given in the front muscles of the thigh. Any subcutaneous leak will lead to necrosis of subcutaneous tissue and skin.

(c) **Intravenous Injection**

600 mg adult dose (10 mg/kg body weight) to be given as I.V. infusion over a period of 4 hours. The dose is repeated at 8 hourly intervals, in 24 hours not more than 1800 mg is given. Quinine should be added to 5% glucose infusion. Loading dose of 7 mg/kg body weight in 200 cc of 5% glucose can sometimes be given over 30 minutes.

(iii) **Absorption and Blood Concentration**

Orally administered Quinine is quickly absorbed from upper intestinal tract and peak concentrations are attained in one to three hours. The absorption from intramuscular injection is sometimes erratic in a serious and complicated case of *P. falciparum* with peripheral circulatory disturbance and the peak concentration time is variable.

With intravenous infusion of 7 mg per kg body weight over 30 minutes or 10 mg per kg body weight over a period of 4 hours, peak concentration is quickly attained.

(iv) **Duration of Action**

The action on parasites starts immediately. Half life of Quinine is 16 to 18 hours. In children half life is shorter-five hours and can cause therapeutic failure. Therefore the dose is to be repeated at 8 hourly interval. If a patient remains seriously ill after third day, intravenous dose should be reduced to aviod toxicity.

(v) **Excretion**

Quinine is completely excreted within 24 hours. The excretion is low in case of renal insufficiency/failure and acute hepatitis. If these complications are suspected, the dose of Quinine should be carefully regulated.

3.2. QUINIDINE

Quinidine behaves almost like Quinine. Loading dose is 24 mg per kg body weight followed by 8 hourly maintenance dose.

Special Considerations

- Both these drugs cross blood brain barrier and are found in cerebro-spinal fluid. The concentration is nearly 7% of the concentration observed in the plasma.
- The blood sugar levels should be monitored regularly in all cases treatmented with Quinine, especially in patients who are on intravenous/intramuscular Quinine administration.

- The cardiac condition should be monitored for adverse effects. However, cardiac complications are not serious in prescribed dosage.

(a) ORAL ADMINISTRATION

(i) Adverse Reactions

Rare after oral administration and usually the following may be observed:--

- Gastric irritation, nausea, giddiness, ringing in the ear (tinnitus), tremors and blurred vision may occur in some patients during the first few days of treatment.
- Idiosyncrasy is seen in some patients but it is rare.
- Symptoms like urticarial or erythematous rashes, itching, subcutaneous or submucous haemorrhages, oedema of eyelids and mucous membrane of lungs; collapse may sometimes follow a single dose.
- Haemoglobinuria and anuria may occur in rare cases of over dose or idiosyncrasy.
- There is a good evidence that those Patients with *P. falciparum* Infection who are exposed to repeated infections and treated with inadequate doses of Quinine, later on when given even a small dose of Quinine develop severe haemoglobenuria—the mechanism of the haemolytic crisis is obscure, though it is probably due to an autoimmune process somehow triggered by Quinine.
- Very rarely unexplained fever occurs or continues after parasitological cure.

(ii) Acute Poisoning Symptoms

- Quinine amblyopia
- Shock
- Hypotension
- Depression of central nervous system, respiratory distress and cardiac arrest

(iii) Chronic Toxicity

On prolonged use of Quinine, the following chronic toxic symptoms are encountered:—

- The symptoms of toxicity and adverse reactions as given above are more pronounced.
- Sudden amblyopia, contraction of field of vision.

Serious impairment of hearing leading to deafness was observed in babies born from mothers who had taken toxic doses of Quinine.

(iv) **Precautions**

- Skin test to detect idiosyncrasy

DRUG SHOULD NOT BE ADMINISTERED ON EMPTY STOMACH

IRREGULAR USE SHOULD BE AVOIDED

(v) **Remedy**

In case of adverse reactions and acute toxicity

- (a) Immediate withdrawal of drug
- (b) Symptomatic treatment

(vi) **Treatment**

Gastric lavage with solution of magnesium sulphate (250 ml at a time, out of the solution of 100 gm magnesium sulphate per litre of water). After lavage it is recommended to leave a dose of 15-30 gm magnesium sulphate in the stomach.

- Artificial respiration
- Parentral administration of ephedrine hydrochloride or emphetamine.
- Intravenous fluids

If the patient can be kept alive for 24 hours, a fatal outcome is generally averted.

- To control ocular disturbances either nicotinic acid 50—200 mg or papaverine 30—60 mg or sodium nitrate 100 mg should be given parentrally.
- The above drugs should not be given when the patient is in shock.

(vii) **Contraindications**

- Drug idiosyncrasy
- History or threat of black water fever

Note: Some physicians do not like to use I.V. or oral Quinine in pregnant women because of its abortificant property. However, in recommended doses in women who have no idiosyncrasy, the chances of abortion with Quinine are negligible. On the other hand, malaria infection can more often precipitate abortion on account of foetal hypoxia.

(b) INTRAMUSCULAR ROUTE

(i) Adverse Reactions

- Fibrotic induration at the site of infection; lasts for a long time.

  Sterile/infected abscess at the site of injection is more common, if proper aseptic care is not taken. This complication is more often observed with Quinine Dihydrochloride as compared to Quinine Hydrochloride.

- Giddiness, tinnitus, tremors, blurred vision, idiosyncrasy, etc.

- Other symptoms as observed with oral administration may also appear.

- Skin necrosis if there is a subcutaneous leak.

- Gangrene and paralysis of area supplied by the artery and nerves, if the injected fluid enters the sheath of arterial or neural plexus.

WITH PROPER PRECAUTIONS THE RISK OF INTRAMUSCULAR INJECTION IS REDUCED BUT NOT ELIMINATED. IT IS NOT RECOMMENDED IN DIABETICS AND PERSONS HAVING CONCOMITANT BACTERIAL INFECTION/SEPTICAEMIA

(ii) Precautions and Remedy

- Proper aseptic measures to be taken to avoid development of problem at the site of I.M. injection.

- Skin-test to eliminate Quinine idiosyncrasy.

- Stoppage of subsequent injections if symptoms develop.

- Symptomatic treatment as indicated under oral administration.

- In case an arterial spasm occurs, the fingers or toes supplied by the artery turn blue and painful. Sometimes there is shooting pain along the course of the artery or nerve in that case the involved site of the injection should be opened and surrounding tissue irrigated with normal saline and dressed with antibiotics and cortisone. Administer peripheral vasodilator to relieve arterial spasm, rest of the symptomatic treatment should be given as required.

(c) INTRAVENOUS ROUTE

(i) Adverse Reaction

- Solutions of Quinine are caustic and if any subcutaneous leak occurs when vein is missed or in case of counter puncture, it will cause intense pain followed by necrosis of subcutaneous tissue and skin.

- Hypotension.

- Fatal collapse as a result of intravenous injection if given too quickly without proper dilution.

(ii) Precautions and Remedy

- Intravenous injection should be given slowly over a period of 4 hours by drip. Daily dose should not exceed 1800 mg in 24 hrs in adults and proportionately adjusted in children.

- Symptomatic treatment for other toxic reactions as indicated under oral administration.

TO AN ADULT QUININE DIHYDROCHLORIDE 420 mg (7 mg/kg BODY WEIGHT) IN 200 CC OF STERILE PYROGEN FREE PHYSIOLOGICAL SALINE OR GLUCOSE 5% TO BE GIVEN INTRAVENOUSLY IN 30 MINUTES WITH INFUSION PUMP AS A LOADING DOSE BUT IT IS RARELY REQUIRED AND SHOULD BE AVOIDED.

4. AMINOQUINOLINE COMPOUNDS

3.3 CHLOROQUINE

(i) Formulations Marketed

Chloroquine is available as sulphate and phosphate salt both for oral and parentral administration.

- Injectible Chloroquine is available both in ampules and vials, the preparation usually contains 40 mg (base) per cc.

- Each tablet contains 150 mg Chloroquine base. The weight of sulphate and phosphate salts in the tablets differ. A Chloroquine phosphate tablet of 250 mg and that of Chloroquine sulphate of 200 mg contains only 150 mg of Chloroquine base.

(ii) **Dosage**

(a) **Oral administration**

It is given as 600 mg each on day 1 and 2 and 300 mg on day 3, thus a total of 1500 mg is given i.e. of 10 mg per kg body weight each on first and second day and 5 mg per kg body weight on third day.

(b) **Intravenous Administration**

Chloroquine is given as I.V. infusion at the rate of 5 mg base/kg body weight over a period of 4 hours. The total dose should not exceed 15 mg/kg b.w. over 24 hrs.

Several dosage schedules for I.V. administration of Chloroquine have been recommended by different authorities. On account of the danger of cardiac toxicity, the above schedule is considered safe and effective.

(c) **Intramuscular Administration**

Chloroquine 3.5 mg base per kg body weight is given at 6-8 hourly interval. However, the intramuscular administration of Chloroquine is not advocated because of its erratic absorption from the site of injection in a serioulsy sick case.

The sudden rise in blood concentration of Chloroquine usually produces equally abrupt severe hypotension and collapse. This reaction is more often observed in children than in adults.

If it is a must to give I.M. Chloroquine, it should be given in two divided doses and blood pressure monitored.

(iii) **Absorption and Blood Concentration**

Chloroquine is readily absorbed after oral administration. The therapeutic concentration is attained within 2 hours. Serum concentration of 15 to 30 ug per litre is minimal inhibitory concentration for *P.vivax* and *P. falciparum*. A dose of 10 mg per kg body weight produces concentration up to 250 ug per litre within 2 hours. With half life of 10 days, concentration once achieved is therapeutically active for 3 to 5 days.

(iv) **Distribution in Tissues**

It is bound to proteins of tissues like spleen, lever, kidney, heart and lungs. Concentration in RBCs is higher than concentration in serum. It crosses transplacental barrier and is also excreted in milk.

(v) **Duration of Action and Excretion**

Chloroquine excretion is very slow. Its average half life is 10 days and may vary from 75 hours to 2 months. It can be detected in urine up to 120 days after administration of a

single dose. The absorption from intramuscular site is very rapid in patients without serious complications. Even with a dose of 5 mg/kg body weight, transient high serum concentration can occur and cause serious complications.

(vi) **Caution**

- Chloroquine has narrow therapeutic index. The lethal single oral dose in infants and toddlers is 1 mg and in case of adults it is 4 gms. Therefore, the drug intake should be carefully monitored.
- The toxicity is nil/minimal at the recommended dose for oral administration.
- The drug is extremely bitter. Therefore, accidental overdose is rare.
- Due to bitter taste it is difficult to administer the drug to infants and young children. Care should be taken not to force the tablet down the throat to avoid accidental asphyxiation.

(vii) **Adverse Reactions**

- Gastric irritation, nausea, vomitting, abdominal discomfort, diarrhoea, headache, pruritis, blurring of vision and hypotension.

(viii) **Reactions in Hypersensitive Persons**

- Other rare reactions like dyskinesia, hearing loss, neuromuscular disorders, photo-sensitisation and even cardio-vascular disturbances are observed.

(ix) **CHRONIC TOXICITY**

Prolonged use of large dosage of Chloroquine for weeks or months may cause:--

- Ocular damage like neuro-retinitis.
- Pigmentations of skin, nail-bed and palate.
- Neutropenia, specially after long continued use.
- Skin rashes.
- Hypotension.

(x) **PRECAUTIONS AND REMEDY**

- DRUG SHOULD NOT BE ADMINISTERED ON EMPTY STOMACH.
- IT SHOULD BE TAKEN ONLY AFTER A MEAL.

- The mild adverse symptoms usually disappear soon after the drug is discontinued.
- The ocular changes are usually irreversible.

(xi) TREATMENT OF OVERDOSE

- Supportive treatment.
- Gastric lavage if patient is not comatosed or in convulsions. Activated charcoal 60-100 gm after lavage.
- Airway protection, assisted ventilation.
- Inj Diazepam up to 10 mg IV slowly if cerebral stimulation is present.
- IV fluids inj Dopamine 200 mg in 500 ml saline, start with 2-5 ug/kg/min. Forced diuresis or urinary acidification increases excretion. Inj Furosemide-20 mg or as required up to 500 mg IV or IM as considered appropriate.
- Charcoal Haemoperfusion in severely toxic patients is beneficial if done at very early stage.

Intramuscular or intravenous use of chloroquine as a routine is not advised because of serious side effects and toxicity such as sudden collapse and hypotension.

3.4 AMODIAQUINE

This compound has action similar to chloroquine.

(i) Formulation Marketed

Amodiaquine is available in the market in the form of oral tablets and is extensively used for treatment of malaria cases by medical profession. The dosage for oral administration its absorption, excretion, etc. are similar to that of Chloroquine. It is suggested that the reader should refer to section on chloroquine.

Amodiaquine appears to retain antiparasitic activity against *P. falciparum* strains resistant to Chloroquine. However, this advantage is shortlived. Therefore, only for very short period of time, it can be used as a second line of drug for treatment of *P. falciparum* strains resistant to Chloroquine.

(ii) Caution -contraindicated for long-term use.

The long-term use of Amodiaquine as a prophylactic drug is contraindicated because one of the metabolites of Amodiaquine, Quinoline, produces acute toxic hepatitis and potentially

lethal Agranulocytosis. This complication occurs 1 in 2000 persons on Amodiaquine prophylaxis. The risk of mortality outweigns the risk of contracting malaria and subsequent mortality. In India, Amodiaquine has been withdrawn from the programme since 1996.

8-AMINOQUINOLINE COMPOUNDS

3.5 PRIMAQUINE

It is one of the compounds of 8-Aminoquinoline group of drugs. It has a better chemotherapeutic index as compared to hypnozoites of P. vivax P. oval and gametocytes of P. falciparum and other Plasmodium species. Its action against persistent tissue phase of malaria phase and gametocytes is unique among antimalarials and no other alternative is available.

(i) Formulation Marketed

It is marketed in the form of tablets of 2.5 mg and 7.5 mg. It is never administered intravenously or intramuscularly and in India no formulation is available for parenteral use.

(ii) Absorption and Blood Concentration

It is rapidly absorbed from the gastro-intestinal tract. Bio-availability of the drug is about 74%. Its therapeutic concentration in the blood is attained within three hours and 150-200 mg per ml concentration is achieved with a single dose of 45 mg. The mode of action of the drug on hypnozoites and gametocytes is not very well known.

(iii) Excretion

The drug is completely metabolised, has a half life of 6 hours and is completely excreted within 24 hours.

(iv) Action

The treatment with Primaquine to achieve radical cure should be given after completing schizonticidal therapy with other antimalarials.

(v) Dosage in Adults

P. falciparum	—	45 mg single dose (0.75 mg per kg body weight)
P. vivax	--	15 mg (0.25 per kg body weight) daily for 5 days.

- In some countries dosage schedule is 0.25 mg per kg body weight daily for 14 or 21 days

- Some authorities recommend administration of 0.75 mg per kg body wt or 45 mg adult dose weekly for a period of 8 weeks. This schedule is considered adequate to achieve radical treatment in cases of *P. vivax*.

(vi) **Adverse Reactions**

- At the recommended dosage, adverse reactions are not likely to occur.

- Anorexia, nausea, vomiting, epigastric distress, abdominal pain and cramps have been observed.

- Passage of dark coloured urine, dyspnoea (difficulty in breathing).

- Methaemoglobibnaemia (manifested by cyanosis of nail-beds, lips, earlobes, tips of nose and tongue).

- More severe toxic manifestations occur in some patients. The hemolytic action of Primaquine is related to the presence of hereditary enzyme deficiency, particularly that of Glucose-6 phosphate Dehydrogenase (G-6-PD): leading to haemoglobinuria and renal failure.

(vii) **Chronic Toxicity**

In addition, there may be bone marrow depression after prolonged use or in cases sensitive to this drug.

- Anaemia, leucopenia.

(viii) **Remedy**

THE ABOVE MANIFESTATIONS DISAPPEAR WHEN THE DRUG IS WITHDRAWN.

- Patient should be removed immediately to the Primary Health Centre. If not controlled the case should be transferred to a referral hospital. In acute and serious cases delay in proper management can lead to fatal consequences.

(ix) **Contraindications and Precautions**

(i) Known G6PD deficient patients, (ii) Infants—because foetal Haemoglobin is more sensitive to 8-Aminoquinolines, (iii) pregnant women, who are high risk groups—primaquine crosses placental barriers and is likely to react adversely with foetal haemoglobin leading to foetal distress, abortion or death, (iv) Patients with tendency to granulocytopenia.

Note:—
PRIMAQUINE SHOULD NOT BE ADMINISTERED ON EMPTY STOMACH TO THE ELIGIBLE PATIENTS

(x) **Poisoning and its Treatment**

- Symptoms may be any one of the listed above.

- Symptomatic treatment like regulation of fluid intake, in case of anuria diuretic like inj Furosemide 20 mg I.V. or I.M. or as required up to 500 mg in 24 hours and in case of acute haemolysis with low Hb% and RBC count, blood transfusion and if kidney failure is observed dialysis should be carried out.

- Supportive treatment like administration of Oxygen and I. V. fluids is carried out whenever required.

IN ACUTE OR CHRONIC TOXICITY FOLIC ACID 10-20 mg. DAILY SHOULD BE GIVEN.

3.6 SULFONAMIDE AND PYRIMETHAMINE COMBINATIONS

There are three long acting sulfonamide compounds namely :—

1. Sulfadimethoxine
2. Sulfamethopyridazine (Sulfalene)
3. Sulfadoxine

The sulfonamides per-se have very little action on malaria parasite. In combination with Pyrimethamine in ratio of 20 : 1 the antimalarial action of both components is potentiated. Comparatively the combination is highly active against *p. falciparum*, but has very little action on *p.vivax*, *p. ovale* and *p. malariae*, their schizonticidal action is slower than that of Quinine, Chloroquine or Artemisinin derivatives.

- This drug combination is used as a second-line of treatment in cases of resistant strains of *P. falciparum*.

Combination of long acting Sulpha and Trimethoprim is not advocated for use in treatment of malaria cases because of wide disparity in the half life of above two drugs.

(i) **Formulation Marketed**

In India it is marketed as oral tablets with different brand names. It is not available in preparation for intramuscular or intravenous administration.

(ii) **Dosage**

The drug is administered orally to achieve clinical and parasitological cure and that too only in cases of *P. falciparum* infection. A single dose (adult) of 1.5 gm is advocated with 75 mg. Pyrimethamine.

The age-wise dosage for radical treatment is given separately.

(iii) **Absorption and Blood Concentration**

Sulfalene (Sulfamethoxypyridazine) and Sulfadoxine are absorbed from the gastro-intestinal tract. Chemotherapeutic blood concentrations are achieved in 4 to 6 hours comparatively they have slower action on malaria parasite.

(iv) **Excretion**

The half life of sulfalene is 65 hours and that of sulfadoxine is 120 to 200 hours. The other component of the combination i.e. pyrimethamine is readily absorbed from the gastro-intestinal tract. Its antimalarial action is similar to chloroguanide, but its potency is greater. Half life is 80 to 95 hours. Therefore, Sulfalene or Sulfadoxine and Pyrimethamine combinations are preferred for treatment of *P. falciparum* malaria.

DIAMINOPYRIMIDINES

3.7 PYRIMETHAMINE

- Apart from the description given above, further aspects are covered below:—

(i) **Adverse Reactions**

- At the recommended dosage the toxicity is very low. Long term administration of pyrimethamine may result in Gastro-intestinal disturbances, ulceration of mouth, loss of hair, and anaemia.

(ii) **Remedy**

- Immediate withdrawal of the drug.
- Administration of Folinic Acid 10-15 mg. daily.

(iii) **Contraindications and Precautions**

USE OF PYRIMETHAMINE ALONE IS CONTRAINDICATED BECAUSE OF RAPID DEVELOPMENT OF RESISTANCE IN PLASMODIUM

- In areas where parasite is resistant to pyrimethamine, it should not be used alone but should be used in combination with long acting Sulpha.

- PYRIMETHAMINE SHOULD NEVER BE ADMINISTERED ON EMPTY STOMACH.

(iv) **Acute Poisoning**

- Acute poisoning has been reported in children who have consumed large number of tablets (100 mg to 250 mg) because of its tastelessness.

(i) **Symptoms**

- convulsions
- loss of consciousness
- sudden hypotension
- collapse

(ii) **Treatment**

GASTRIC LAVAGE, INJ DIAZEPAM 5-10 mg GIVEN SLOWLY BY INTRA-VENOUS OR INTRAMUSCULAR ROUTE FOLINIC ACID 10-20 mg SHOULD BE GIVEN DAILY.

SULFONAMIDES

3.8 LONG ACTING SULFONAMIDES

Long acting Sulfa (like Sulfadoxine, Sulfalene) with Pyrimethamine combination is used in areas where *P. Falciparum* has developed resistance to chloroquine.

The above combination of drugs if given in recommended dosage is generally well tolerated, however, the following adverse or toxic manifestations may be encountered.

(i) **Adverse Reactions**

- Gastro-intestinal disturbances like nausea and vomiting.
- Mild jaundice—urticarial, erythematous, maculopapular morbilliform or purpuric skin rashes.

(ii) **Long Term Toxic Effects**

Haematological:—granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura.

- Steven - Johnson syndrome.

- Because of irreversible complications mentioned above, its use as chemoprophylaxis is contraindicated.

(iii) **Remedy**

- Immediate withdrawal of drug.
- Plenty of fluid intake.
- Folinic acid 10 to 30 mg daily.

(iv) **Contraindications**

The drug should not be administered during first three months of pregnancy or to infants and to patients who are hypersensitive to drug.

(v) **Caution**

- Long acting Sulfa should not be given on empty stomach.

3.9 MEFLOQUINE

Mefloquine is a compound of Aminoquinolinemethanol group and is related to Quinine. It is long acting and potent blood schizonticidal. It acts against all species of malaria parasite. It is preferentially used for the treatment of *P. falciparum* strains resistant to Chloroquine and is effective as a single dose.

(i) Formulation Marketed

Mefloquine is available in 250 mg tablets for oral administration. There is no parenteral formulation of drug and cannot be used as I/V or I/M injections since it is irritant to peripheral arteries and veins.

(ii) Dosage

Dose of Mefloquine is 15 mg base per kg body weight as a single dose i.e. three tablets (adult dose) are administered at a time (some countries use 1 gm base as a single dose in an adult for treatment of resistant strains of *P. falciparum*).

(iii) Absorption

Mefloquine is absorbed from the gastro-intestinal tract and biotransformed in the body. It does not cross blood brain barrier; therefore, it is not much suitable for the treatment of cerebral malaria cases.

The half life of the drug is 6 to 30 days or more. It is mainly excreted in urine. Nearly 5% of the drug being used is excreted in bile and faeces. It binds extensively with plasma proteins and thus has a longer half life.

(iv) Adverse Reactions

- Nausea, vomiting, diarrhoea, abdominal pain, more common if given in dose higher than 15 mg per kg BW.

- Asymptomatic sinus bradycardia and marked sinus arrhythmia. Pulse rate decreases 3 to 4 days after drug administration and returns to normal within two weeks.

- Predictable sensation of light headedness often accompanied with dizziness and difficulty in concentration occurring within few hours (4-6 hours) after first dose and resolving within a few days.

- Rare reactions include myalgia, hair loss, visual disturbances, palpitation, feeling of weakness, erythema multiforme major, transient elevation of transaminases and granulocytosis.

- More serious central nervous system side effects are abrupt psychosis, loss of consciousness or even generalised convulsions. It occurs in second week after starting of prophylaxis and resolves during next two weeks if drug is stopped. The central nervous system reaction is not dose dependent, sometimes single dose can precipitate such type of reactions.

(v) **Precautions**

- Both Quinine and Mefloquine are cardiotoxic. Mefloquine concentration can rise abruptly after cessation of Quinine administration. Caution should be exercised when both drugs are used sequentially.

(vi) **Contraindications**

- Mefloquine should not be used for prophylaxis in persons involved in tasks requiring fine co-ordination and spatial discrimination.

(vii) **Use in Pregnancy**

- Its administration for treatment of acute malaria episode should be avoided in first trimester of pregnancy.

3.10 FANSIMEF

Mefloquine, Long Acting Sulpha and Pyrimethamine Combination

Initially the combination of mefloquine, long acting Sulfa and Pyrimethamine was recommended for use because of its presumed superior action and in order to delay development of *P. falciparum* strains resistant to Mefloquine.

It was observed that this combination of Mefloquine and long acting Sulpha + Pyrimethamine had a number of serious adverse reactions like skin reaction, involvement of ocular system, gastro-intestinal disturbances as well as serious neuro-psychiatric complications. The efficiency of this combination was more or less similar to Mefloquine alone without any other advantage.

This combination is no longer recommended either for treatment or prophylaxis of malaria infection.

As the combination of drugs should have a similar half life and since no other antimalarial drug has long half life of 30 days as Mefloquine, the next best combination of Sulfadoxine and Pyrimethamine was selected.

3.11 HALOFANTRINE

The drug belongs to phenanthrenemethanol group. It was registered in 1988 for treatment of malaria.

It is effective against *P. falciparum* strains resistant to Chloroquine and Pyrimethamine +Sulfadoxine. It has schizonticical activity against all species of malaria parasite i.e. *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*.

(i) Formulation Marketed

The drug is marketed as tablets containing 250 mg. Halofantrine Hydrochloride (233 mg. Base). Intravenous or intramuscular preparation is not available.

(ii) Dosage

Children	—	8 mg per kg body weight 3 doses at 8 hourly interval.
Adult	—	500 mg or 8 mg kg body weight three doses at 8 hourly interval.

(iii) Absorption and Blood Concentration

It is completely absorbed from gastro-intestinal tract. Maximum plasma concentration is reached in 6 hours after a single dose. Its absorption from the gastro-intestinal tract is erratic probably due to its lipid solubility. Even with therapeutic dose, the peak plasma concentration levels are variable and cumulative toxicity has been observed, sometime leading to fatal outcome. On account of the above behaviour of the drug, it is not recommended for treatment of complicated *P. falciparum* malaria cases. It has also shown cross-resistance to Mefloquine.

(iv) Adverse Reactions

- Generally mild and transient, not requiring specific treatment
- nausea, vomiting, diarrhoea and abdominal pain (15-25% cases)
- Vomiting occurs approx. 1 hr after administration
- Orthostatic hypotension (33% cases)
- prolongation of QT interval, it is a dose dependent effect
- Transient increase in serum transaminase

(v) Contraindications

- Pregnancy and lactating mothers

3.12 QINGHAOSU DERIVATIVES

Artemisinin is the name given to active principle of Qinghaosu (*Artemisia annua*). It is poorly soluble in water and decomposes in other solvents. It is produced as dihydroartemisinin and is commercially marketed.

(i) Formulations

Three formulations of the derivatives of Qinghaosu are available:—

(a) Artemether

Artemether is marketed as methylether of dihydroartemisinin. It is available in oil preparation of one cc ampule containing 80 mg for intramuscular use.

(b) Artesunate

Artesunate is a water soluble derivative, it can be administered parenterally in aqueous solution. It is also marketed in tablet form containing 50 mg of the compound.

(c) Arteether

It is similar to Artemether compound

(ii) Dose

1.	Artemisinin	—	500 mg daily for five days.
2.	Artesunate	—	60 mg at 0,4,24 and 48 hours.
3.	Artemether	—	80 mg daily dose—total of 480 mg over five days, first dose being double.

(iii) Absorption and Blood Concentration

After intravenous administration, the peak concentration is achieved immediately. After oral administration, the peak concentration is attained within 1 hour. The half life of the drug is 45 minutes in case of Artesunate and up to 6 hours in case of Artemether. Because of short half life, repeated doses are required at frequent intervals.

Its efficacy of drug lies in the treatment of resistant strains of *P. falciparum* especially in cerebral malaria cases where its action is faster as compared to that of Quinine. The drug should be used very cautiously although it is less toxic than quinine there is high recrudescence rate with therapeutic schedule given above.

(iv) **Adverse Reactions**

No significant clinical adverse effect was observed in more than 2000 malaria patients treated with the drug during field trials.

- Transient reduction in reticulocytes and neutrophil granulocytes, especially young forms.

- Transient increase in transaminase

(v) **Use in Pregnancy**

- Controversial

- Contraindicted in first trimestering of pregnancy. In animal experiments it was observed to be absorbed by the foetus

Adequate data is not available regarding its side effects under Indian conditions.

Table-3.3—SUMMARY OF DOSAGES OF ANTIMALARIAL DRUGS

Name of Drug with Chemical Group	Year of Discovery	Year when used as an Antimalarial	Internationally accepted adult dosage	Half life
1	2	3	4	5
(1) CINCHONA ALKALOIDS	Formula in 1908 Synthesised in 1948	1940s	600 mg. 3 times a day for 7 days 600 mg. I./V. or 10 mg kg. B. W. over 4 hours Repeated 3 times in 24 hours for CEREBRAL MALARIA	10 hrs
(2) BIGUANIDES				
(a) Proguanil	1944	1945	300 mg. twice daily	24 hours
(b) Chlorproguanil @	1960	1960s	20 mg. daily	
(c) Cycloguanil	1965	1965	Injectable-140 mg/ml. 2-2.5 ml Intramuscular	
(3) DIAMINO PYRIMIDINES				
(a) Pyrimethamine	Early 1940s	1952	50 mg daily for 3-4 weeks usually combined with other drugs.	96 hrs
(b) Trimethoprim @	Late 1940s	1950s		16 hrs.
(4) 4-AMINOQUINOLINES				
(a) Chloroquine	1934	Late 1940s	600 mg first dose after 6-8 hours 300 mg followed by 300 mg daily for next 2 days. Alternatively- 600 mg first day 600 mg second day 300 mg third day	3-7 days (Traces found in urine) up to 3 weeks
(b) Amodiaquine	—	—	Total dose 1400-2000 mg	

1	2	3	4	5
(5) 8-AMINO QUINOLINES				
(a) Primaquine @	1920	1952	15 mg daily for 14 days for *Pv.*	10 hrs.
(b) Pamaquine @	1924	1952	45 mg a single dose for *Pf.*	
(c) Quinocide	1952	1952		
(a) Sulfalene 500 mg & Pyrimethamine 25 mg. (one tablet)	1970s	1970s	1500 mg Sulfalene 75 mg Pyrimethamine (Single dose)	
(b) Sulphadoxine 500 mg & Pyremethanine 25 mg. (one tablet)	1960	1960	1500 mg of sulphadoxine 75 mg. Pyremethanine (single dose)	
(8) ANTIBIOTICS				
(a) Tetracycline	1950s	1952	250 mg to 500 mg 6 hourly for 10 days	6 to 9 hrs
(b) Minocycline @	1960s	1960s	100 mg 4 times a day	
(c) Clindamycins @	1960s	1960s	150 mg 4 times a day	
(d) Doxycycline	—	—	100 mg once or twice a day for 7 days.	
(10) MEFLOQUINE (4-Quinoline methanols)	1970s	1970s	750 mg. single dose.	
(10) QINGHAOSU	168 B. C.	1972		
Artemisinin	—	—	500 mg/day × 5 days (8 mg/kg body wt.)	
Artemether	—	—	160 mg I. M. 80 mg OD Total 640 mg (3.2 mg & 1.6 mg per kg. body wt.)	4-11 hrs

1	2	3	4	5
Artesunate			120 mg 60 mg. 12 hourly Total 640 mg. (2 mg & 1 mg/kg/body wt.)	4 to 8 hrs
(11) Halofantrine-1988	—	—	500 mg 6 hourly × 3 days (8 mg/kg body wt. 6 hourly)	1 to 3 days.
@ s DRUG NOT USED GENERALLY OR NOT USED ALONE FOR TREATMENT USED IN COMBINATION WITH QUININE				
(6) SULFONAMIDES				
@ (a) Sulfadiazine	1930	1940s *	250 mg three times a day	5-6 days
(b) Sulfamethoxyine-	—	—		
(c) Sulfamethoxy pyridazine*	1950s	1950s	250 mg daily single dose for 5-6 days	100-120 hrs.
-Sulfalene*				
(d) Sulfadoxine	—	—	—	65 hrs

* Recommended for use only in combination with pyrimethamine

SECTION-II

PRINCIPLES FOR EVOLVING NATIONAL ANTIMALARIAL DRUG POLICY

1. Definition

In 1988, WHO defined the National Antimalarial Drug Policy as "a set of recommendations and regulations concerning antimalarial drugs and their utilisation in the country". The National Antimalarial Drug Policy should be a part of National Drug Policy and also contains a set of guidelines for use of antimalarials by medical profession and National Malaria Control Programme.

2. Need for Drug Policy

It is a known fact that Chloroquine is a versatile antimalarial drug. Under normal circumstances, it acts against all stages of schizogony and immature gametocytes of malaria parasite. When introduced for the first time in an area, it produces clinical as well as parasitological remission in 98 to 99% cases of malaria infection within 72 to 120 hours. With a rational use of Chloroquine, chances of selecting a resistant strain are very meagre. If Chloroquine therapy is coupled with effective transmission control operations, the resistance may not appear for a couple of decades or even more. On the other hand indiscriminate use of irrational drug schedule, chemotherapeutically ineffective dosage, poor drug compliance during chemoprophylaxis tend to select out resistant strains of *P. facliparum* within a short period of time. There are several hypotheses regarding appearance of drug resistance in malaria parasites. Most plausible theory is that like population of other living organisms *P. falciparum* population also has a very small proportion of viable mutants. Some of these mutants have an alternate metabolic pathway to withstand the action of antimalarial used for treatment of a malaria case, as a result of sensitive parasites are killed and the viable mutants with alternate metabolic pathway survive and multiply, thereby *P. falciparum* strains resistant to Chloroquine or other antimalarials are selected. The resistant strain is more likely to be selected in insurgent areas or in transmigratory population groups where, on account of unsettled conditions, there is

indiscriminate use of the antimalarials like Chloroquine, Long acting Sulpha and Pyrimetha mine combination, i.e. most of them have long half life. At the tail end of the blood concen tration, the drug level is chemotherapeutically ineffective. During this period, the mutants survive and multiply. This population of resistant strain is then locally transmitted and gets established. The resistant strains are usually not selected against the drugs with short half life because of frequent administration of dosage to attain clinical and parasitological cure and thereby the chemotherapeutically ineffective blood levels are for a very short period of time only and next dose of the drug again elevates the blood concentration to therapeutically effective levels.

It is seen that *P. falciparum* strains show resistance to Chloroquine while the tolerance is exhibited by *P. vivax* to some of the antimalarials. As such, there is an urgent need to have National Antimalarial Drug Policy to rationalise the approach to malaria chemotherapy. This aspect gains paramount importance in the light of the fact that in some of the South East Asian, African and South American countries, *P. falciparum* has shown resistance to second line of antimalarials within a very short period of time after their introduction for general use in the country. In India, the situation is not so urgent. The degree of resistance in *P. falciparum* resistant strains to the second line of antimalarial drugs is very low and the foci are limited.

3. Selection of Antimalarial Drug—Options Available

As already mentioned, the endemic countries should recognize the fact that resistance to the antimalarial drugs will ultimately develop when they are used extensively for treatment of uncomplicated *P. falciparum* malaria. When the first line of drug, usually Chloroquine becomes increasingly ineffective, it should be changed before there is a significant rise in incidence of malaria with high morbidity and mortality. The policy requires consideration of not only drug resistance and efficacy of antimalarials but also the target population, immunity levels, compliance with treatment schedules, cost of the new drug and its availability.

The WHO document on Antimalarial Drug Policy (March, 1994) has given two case studies on antimalarial drug policies of Malawi and Thailand.

In Malawi, there were reports of drug failure in *P. falciparum* cases with Chloroquine at a dose of 10 mg per kg body wt. It was confirmed that parasitological clearance by Day 7 was not obtained in 84 per cent of cases. When the dose was increased to 25 mg per kg body wt. it affected clinical cure in 92% of the cases but failed to clear parasites in half of the cases

Malawi Government formulated a malaria treatment policy and recommended Chloroquine as the first line of drug for treatment of malaria cases. For treatment of malaria cases not responding to Chloroquine, antimalarials like sulfadoxine plus Pyrimethamine or Amodiaquine were reserved as second line of treatment, while Quinine was recommended for treatment of complicated Malaria cases. Although R III level of resistance to Chloroquine has risen, there is no resistance to Sulfadoxine and Pyrimethamine as yet—1993 report. The other determinants for change of drug policy in Malawi were consumer pressure, competitive cost and compliance to drug schedule. A single dose of tasteless Sulfadoxine + Pyrimethamine had facilitated drug compliance by the population in general.

In Thailand, resistance to Chloroquine and the antimalarials has developed more quickly. On finding Chloroquine resistant strains of *P. falciparum*, the Sulfadoxine + Pyrimethamine was introduced. The adult dose was 1 gm. It replaced Choloroquine as a first line of treatment of *P. falciparum* infection in 1973. It was effective in checking malaria morbidity and mortality over next 7 years. Later on, there were reports of drug failure. The dose was increased to 1.5 gms. The efficacy of Sulfadoxine - Pyrimethamine gradually decreased. Quinine and Tetracycline became first line of treatment.

The experience on the use of different antimalarials as a first line of treatment to *P. alciparum* cases necessitated differentiation of areas based on the response differed widely throughout the country. The introduction of alternative drug after *P. falciparum* exhibits resistance to currently used drug without measures for transmission control or ensuring proper drug compliance leads to selection of resistant strains more quickly and morbidity and mortality rates increase. The quick emergence of resistance in Thailand to antimalarials successively used as first line treatment was basically due to indiscriminate and irrational self-medication by illegal gem miners on Thai-Kampuchean Border where transmission control activities were nonexistent.

In India, the recent drug policy lays down that Chloroquine should be used for first line of treatment all over the country and even in areas showing R II and R III level of resistance. The drug schedule has been changed in selected pockets showing R II & R III levels at 25% or above in a minimum of 30 cases studied. Here the second line of drug will be long acting Sulpha and Pyrimethamine combination. Quinine is the drug of choice for treatment of complicated malaria cases. The details of National Drug Policy of India are given in subsequent section.

4. Aims and Objectives

4.1 The Primary aim of the drug policy should be to ensure prompt clinical and pa rasitological cure in a malaria patient. This primary purpose is encompassed in the basi technical elements of the WHO Global Malaria Control Strategy (WHO 1993). The clinica and parasitological cures are defined as:—

(a) **Clinical remission**—i.e. clearance of signs and symptoms of malaria within a reaso nable period of time in the patient under treatment.

(b) **Clinical cure** is remission of signs and symptoms of malaria plus prevention of re crudescence i.e. nonappearance of signs and symptoms within 14 days following the completion of treatment.

(c) **Parasitological cure** entails elimination of all stages of parasites from the body i.e. liquidation of all stages of schizogony and gametocytes as well as hypnozoites in case of *P. vivax* and *P. ovale*.

4.2 (a) *The first objective* Prompt treatment can be defined as administration of effec tive antimalarial drug schedule to a patient suffering from malaria on his first contact with peripheral health worker or medical facility. The prompt treatment should also aim at preventing further serious complications in the patient and ensuring prevention of further spread of infection.

(b) *The second objective* of the National Antimalaria Drug policy is to minimise the selection pressure of the antimalarial drug to prevent emergence of drug resistant strains. Although it is classified as second objective, it is even more important than any other objective because of availability of only a limited number of antimalarial drugs for treatment of malaria cases. The treatment is further restricted on account of the high cost of the new antimalarials their serious side effects, complex and longer dosage regimen necessitating careful monitoring of the case.

Actions required

(i) To fulfil this objective, the medical profession should be given complete orientation in selection, use and dosage schedule of antimalarial drugs. The limited knowledge concerning the use of antimalarial drugs and irrational use of dosage results in selection of resistant strains.

(ii) Further, it is necessary to have full control on drug distribution and their availability to the medical profession to avoid indiscriminate use of new antimalarials as well as self administration by the individuals.

(iii) It is possible that the restrictions on distribution and availability of specific antimalarials, the rigid control on optimum dosage of antimalarials, for achieving complete clinical and parasitological cure thereby bringing uniformity of treatment in ma laria cases are likely to be resisted by physicians because of their option to use antimalarials for treatment of malaria is restricted by such a policy.

(iv) These restrictions are essential and beneficial, since in the long run, they prevent emergence of resistant strains of parasite. They are all the more necessary as the number of antimalarials available at this juncture is limited.

The components to meet the objective of National Antimalarial Drug policy should be :—

(a) Selection of suitable antimalarials out of the total number of antimalarials available for the treatment of infection with different species of malaria parasites.

(b) To lay down the guidelines for use of antimalarials registered in the country for treatment of malaria cases.

(c) Promulgation of regulation specifically with regard to second line of drugs, their prescriptions, fixing the outlets for sale, distribution to the community and utilisation by medical profession.

(d) It is necessary to make antimalarials available to the community at an affordable price, therefore, price regulatory mechanism should be developed by the National Government in respect of antimalarials. If required, the prices may have to be subsidised.

(e) As all antimalarials are not manufactured in the country, a long-term policy for their import or manufacture in sufficient quantities to meet the requirement by the National Malaria Control Programme and medical profession should be formulated. This policy should ensure uninterrupted availability of antimalarial drugs suited to meet the country's requirements.

(f) It is necessary to lay down the rules for regulating quality of antimalarials.

(g) A regulatory mechanism for distribution system should ensure availability of drug on demand across the sale counter or the National Malaria Control Organisation, as required across the sale counter or the National Malaria Control Project.

(h) In the light of the emergence of resistant strains of *P. falciparum*, it has become necessary that the National Drug Policy should specify the second line of treatment for uncomplicated malaria case(s) when the first line of treatment fails.

(i) The policy should also lay down guidelines for treatment of complicated malaria cases i.e. *P. falciparum* presenting with serious signs and symptoms.

(j) Pregnant women, who are at high risk of contracting malaria, should receive regular and prompt treatment. The Drug Policy should spell out the procedure to be adopted for treatment of pregnant women and also lay down guidelines for prevention of malaria amongst them.

(k) The Government should enact regulations to enable the physicians authorised to prescribe second line of antimalarials and the outlet for such drugs to minimise their misuse.

(l) The regulations should be promulgated specifying the health services i.e. Fever Treatment Depot, Malaria link Volunteers, Multipurpose Workers, Primary Health Centres, Dispensaries, Peripheral Hospitals and Referral Hospitals. These agencies would advise the malaria patient suitable line of treatment. The decision to make particular drug available through specified outlet should be made after considering the diagnostic and therapeutic facilities available at every health facility cited above.

5. Price Regulations

The National Government should ensure that the price of essential antimalarials necessary for treatment of Plasmodium infection are so regulated that they are affordable by the general public. If necessary the industry should be subsidised, so as to keep the price of antimalariais within the reach of common man.

If the price of antimalarials becomes exorbitant, a large portion of the community will not be able to afford the treatment or they may take only partial treatment. Under the circumstances, chances of selecting resistant strains of the parasite to the drugs will increase. Therefore, the cost of the antimalarials to the consumers should be so regulated that even a common man can afford it. Cost structure is not being suggested because the cost of antimalariais in India or other countries would vary with inflationary process.

6. Regulations on Supplies and Distribution

The misuse of antimalarials is likely to select a resistant strain within a short span of time. For example indiscriminate use of a new drug such as Mefloquine will precipitate resistance within a period of 3 to 4 years. There should be specific regulations and laws concerning import, manufacture, quality control and distribution by fixing outlets and restrictions on sale of antimalarials through proper authorisation and prescription.

The National Drug Policy will differentiate in procurement and supply of different antimalarials.

(i) Drugs for first line of treatment of malaria infection should be made widely available through all health care outlets and even through the market sources. This category should include drugs like Chloroquine, Quinine, Primaquine, Tetracycline, Doxycycline, etc.

(ii) The second line of drugs should be reserved for treatment of drug resistant strains of malaria parasites. Regulations for use of these drugs should be more stringent. The drug should be made available only through specific outlets at a specified health facility and based on prescription of a qualified medical practitioner. Drugs like long acting Sulpha+ Pyrimethamine, Mefloquine, Artemisinin and its derivatives fall under this category.

(iii) An Expert committee should decide whether in the light of the status of *P. falciparum* resistance to Chloroquine, it would be necessary to introduce any of the above drugs and if so, in which part of the country and what should be the regulatory mechanism for use of the drug etc. Under the Indian conditions, taking into consideration the status of *P. falciparum* resistance to Chloroquine its distribution and presence of R II and R III level of resistance, the National Drug Policy was reviewed by an expert committee in the year 1995.

7. Choice of Antimalarial Compounds for Malaria Chemotherapy

A. TREATMENT OF UNCOMPLICATED MALARIA

For treatment of fever or clinically diagnosed malaria case

(i) First Line of Drugs

In a new area or an area with sensitive strains of *P. falciparum* :—

Treatment category	Antimalarial of choice	Type of cure
– Presumptive treatment (before microscopic confirmation)	Chloroquine Single dose	Clinical and parasitological remission achieved in malaria infections with all species
— Radical treatment (after microscopic confirmation)		
(a) *P. falciparum*	Chloroquine Single dose + Primaquine Single dose	Complete parasitological cure obtained
(b) *P. Vivax P. malariae P. ovale*	Chloroquine Single dose + Primaquine. for 5/14 days	Complete Parasitological cure achieved, gametocytes and hypnozoites are also liquidated.

(ii) Second Line of Drugs

In areas with *P. falciparum* strains resistant to Chloroquine.

– Presumptive treatment (before microscopic confirmation)		
(a) In areas with 50% or more *P. vivax* infection and *P. falciparum*.	Chloroquine Single dose or 3 doses	Clinical cure in most cases

R II/III % levels are low (below 25 %)		parasitological remission in *P. vivax* observed

The criteria for high or low percentage of R II & R III to be decided by National Government Generally if R II and R III combined together against an antimalarial level of resistance is 25 % or more than a change to alternative drug is recommended.

(b)	In areas with *P. falciparum* predominance and R II/R III percentage levels are high (25 % or above)	Chloroquine single dose + long acting Sulpha and Pyrimethamine	Clinical and parasitological remission achieved in malaria infection with all species.

- Radical treatment

(after microscopic confirmation)

(a)	*P. falciparum*	Long acting Sulpha and Pyrimethamine combination Single dose+Primaquine Single dose.	Complete parasitological achieved.
(b)	*P. vivax, P. malariae* and *P. ovale*	Same as first line of drugs i.e. Chloroquine . Single dose+Primaquine 5/14 days	Complete parasitological cure achieved.

(iii) Third Line of Drugs

In areas where *P. falciparum* is resistant to both Sulpha and Pyrimethamine combination and Chloroquine.

Presumptive treatment (before microscopic confirmation)	Mefloquine Single dose	Clinical and parasitologic remission achieved in malar infections with all species.

If Mefloquine is not available, Amodioquine in three doses can be used for few years Mefloquine should be used cautiously because of the danger of early selection of resistan strains of *P. falciparum*.

Radical treatment

(after microscopic confirmation)

(a)	*P. falciparum*	Mefloquine Single dose or Quinine for 7 days + Tetracycline for 10 days + Primaquine Single dose after completing Quinine therapy	Clinical and parasitologica cure obtained.
(b)	*P. vivax* *P. malariae* & *P. ovale.*	Same as first line of drugs i.e. Chloroquine Single dose + Primaquine 5/14 days	Complete parasitological cure achieved.

B. TREATMENT OF COMPLICATED MALARIA WITH *P. falciparum* INFECTION

Start antimalarial on clinical diagnosis, without waiting for microscopic result Examine serial blood slides at 6 hourly interval for monitoring response.

Primary Treatment	Quinine I/V till the patient regains consciousness, continue oral Quinine total duration 7 days or I/V Artemisinin e.g. Artisunate or Artemether	Achieves clinical and parasitological remission
Radical treatment (after microscopic confirmation)	Oral Primaquine Single dose	Complete parasitological cure obtained

8. Packaging of antimalarials

In India, normally the antimalarials are strip packed for sale across the counter. The bulk packing in tins of 1000 tablets each is done for supply to the hospitals and National Malaria Anti Programme (NAMP). In the hospitals, the issue of antimalarials from the bulk supply is usually well regulated and consumed within the expiry date. Under NAMP, the supplies are procured through Medical Store Depots by Logistics incharge at the national level. The State Malariologists on receipt of requirement at the State Headquarters, in turn allot antimalarials to the District Malaria Officers. From there, these antimalarials are further despatched to the Primary Health Centres. Distribution of antimalarials from the stores of the PHC to the MPWs is generally satisfactory. However, it has been observed that the Fever Treatment Depots and the Drug Distribution Centres are given tablets in packed tins. Drug Distribution Centres are given tablets in packed tins of 1000 tablets, although instructions are there to give 200 tablets at a time and replenish them whenever required. The disadvantage of the dumping of a large number of tablets at these health posts is that when a DDC or FTD becomes defunct, these tablets are not utilised and inflict loss to the programme. It would be advisable to procure supplies in smaller packings of suitable size for use by the peripheral voluntary agencies. Alternatively they can be repacked in smaller containers preferably in 200 tab. containers by the State or District authorities as may be logistically convenient.

9. Marking on Tablets

The tablets packed in strips do not require separate markings but the tablets shou be line marked as some of them may have to be split for administration of smaller doses t children.

The bulk purchases made by NAMP should be marked suitably to indicate that th tablets have been supplied to the NAMP. They should also be scored for breaking them int smaller pieces to facilitate administration of lower doses to the children.

10. Quality Control

It is absolutely necessary to maintain the quality of antimalarials. For example — if base contents vary in each tablet by ± 10% the dose of 600 mg. Chloroquine will be reduced to 540 mg per dose or increased to 660 mg. In case of infants and children, because of low chemotherapeutic index of Chloroquine, serious complications may arise if the contents are not standardised. It is suggested that in all antimalarial tablets used for treatment of malaria, the base content should be within ± 2%.

Every batch of the drug should be tested for quality control by the medical store depots. After the supply is effected to the central organisation, they should independently carry out the quality control of the drug. Similarly at state level, quality control should be repeated before the drug is distributed to the periphery.

In case the drug failure is observed by the peripheral medical officer, the first task of the medical officer should be to send drug samples taken out of the container from which the treatment was given, for quality confirmation to the laboratory designated by the State Government or as per the guidelines issued by the appropriate authorities. The State Government can select reputed laboratories within the State for this purpose and make a standing arrangement with them to test the drug samples sent from the periphery by authorised medical officers on priority. Suitable arrangements for payment of fee for testing the drug should be made so that the sample testing is not delayed for want of funds. The test report should be made available within a short time but not later than 30 days.

11. Shelf Life

The bulk procurement of antimalarials should be distributed in such a manner that it can be consumed at the peripheral level before the date of expiry. The Procurement Officer should consider the time taken from the date of procurement, till the allotment to the States likely delay in distribution to the districts and later to the periphery and thereafter its ultimate administration to a malaria case. This period is usually 3 to 9 months.

12. Storage Instructions

The antimalarials should be stored in air tight containers. Exposure to humidity and heat should be avoided especially in case of sugar coated tablets. The strip packed tablets do not require elaborate precautions for storage. However, the plastic coated strips are usually nibbled by rats and cockroaches. Therefore, the strips should be stored in places free from rodents.

13. Estimates of Requirement

13.1 Requirement of Chloroquine

In NAMP, Chloroquine is the drug of choice. It is used all over the country except in few selected areas (with approximately 25 million population) where second line of drugs are administered.

The requirement of Chloroquine is calculated as follows:

$$\frac{\text{Total population} \times \text{Local fever rates}}{100} \times 3 = \text{Total No. of tablets required.}$$

At the national level, taking 900 millions as the population of the country in 1995, and average fever rate as 15% for the country as a whole, the requirement of the antimalarials will be:—

$$\frac{900 \times 15}{100} \times 3 = 405 \text{ million tablets.}$$

This quantity can be suitably distributed to the States on the basis of their own estimates of fever rates. Out of this quantity, sufficient number of antimalarials can be given to FTD's because the 15% fever cases are screened by FTD's, DDC's peripheral health workers and medical institutions all put together.

13.2 Requirement of Quinine

As already mentioned in previous chapters, out of total *P. falciparum* cases. Only 0.5% to 2% go into serious complications requiring treatment with Quinine injections. Therefore, at the national level, the requirement can be calculated as under :—

$$\frac{\text{Total } P.\ falciparum \text{ cases} \times 2 \times 9}{100} = \text{Ampules of Quinine injection required}$$

*Nine ampules are sufficient for a period of three days. It is administered intravenously. It is expected that during this period patient will come out of coma and will be able to take oral antimalarials. If the response is delayed and patient remains comatosed after three days, carefully evaluate the clinical condition as the delayed response may be due to some other pathology.

After the Injection Quinine complicated case of *P. falciparum*, the patient regains consciousness or is able to take oral tablets, the Quinine therapy schedule of seven days should be completed with oral administration. Requirement for tablets is calculated as under :—

$$\frac{P.\ falciparum \text{ cases} \times 2 \times 18}{100} = \text{Total no. of Quinine required}$$

The distribution of *P. falciparum* is not uniform in the country. Each State should calculate the requirement on the basis of *P. falciparum* cases recorded in the State and the indent should be placed with the Central Organisation depot well in time. i.e. one year in advance to facilitate procurement and supply.

13.3 Requirement of 8 Aminoquinoline

8-Aminoquinoline is procured in tablets of 2.5 and 7.5 mg. The estimates should be based on the number of positive cases detected in the community taking into consideration, both *P. vivax* and *P. falciparum* cases. The calculation done is as under:—

Total number of positive cases × 8=Total number of 8 AQ tablets required.

The total procurement should be divided equally between 2.5 mg. and 7.5 mg. tablets.

Some of the formulations of 8 Aminoquinoline are sugar or lacquer coated, these tablets require special storage facilities.

13.4 Requirement of Long Acting Sulpha

The requirements of long acting Sulpha should be based on the population where second line of treatment is administered to *P. falciparum* cases under the National Drug Policy, estimates are made by taking into account:—

Number of *P. falciparum* cases recorded in the locality. } × 3=Total tablets required

13.5 Rough Estimates of buffer Stock

Around 20 to 25% of annual requirement of all antimalarial tablets or injectables should be kept as a buffer stock to meet the requirement of pipeline and emergent situations.

The buffer stock of the previous year should be utilised in the beginning of the year through suitable distribution. Current buffer stock should be built up from fresh supplies.

13.6 Reserve Stock for Epidemic Control

Apart from these minimum requirements, there should be a provision for drugs in the pipeline as well as buffer stock to meet the emergent requirement of the epidemic areas. It must be kept in mind that the procurement process i.e. making estimates of requirements,

getting financial sanctions, placing procurement orders with the manufacturers, flow of supplies being dependent on the firm's manufacturing capacity and ready stocks held by them usually delays availability of drugs. Under these circumstances it is not possible to make available the drugs by bulk purchases or even local purchase for use in epidemic areas at a short notice. The drugs should be made available immediately within three days to the epidemic areas to prevent high morbidity and mortality. Therefore, it is necessary that the buffer stock should be held at district level for use in case of epidemics/focal outbreaks.

SECTION - III

NATIONAL ANTIMALARIA DRUG POLICY (INDIA) 1995

The National Antimalaria Drug Policy was first drafted in 1982 to combat the increasing level of resistance to Chloroquine detected in *Plasmodium falciparum*. Thereafter the drug policy was being reviewed periodically based on the drug sensitivity studies. In the wake of recent large scale epidemics of malaria in different parts of the country accompanied by high mortality, the question of availability of antimalarials and treatment policy of malaria cases was under debate in many quarters including the medical profession.

To look into these aspects of malaria chemotherapy, a Committee of medical experts from different specialities clinical pharmacology, malarialogy, etc. was constituted by the Director General of Health Services under his chairmanship.

The committee deliberated on various aspects of malaria chemotherapy such as (i) availability of antimalarials at national and international levels, (ii) pharmaco-dynamics of antimalarials, (iii) resistance to different species of malaria parasite especially *P. falciparum* to antimalarials, the distribution and magnitude of the problem in the country and (iv) response of the Indian strains of *P. falciparum* to different antimalarials.

After extensive discussions on the information made available by the Directorate of National Malaria Eradication Programme, Malaria Research Centre (MRC) and review of National and International experiences along with the opinion of clinicians and pharmacologists, the Committee observed that:—

Presently the following antimalarials are available but their use is determined on the basis of the action of each antimalarial against a particular species of Plasmodium and its stages, rapidity of action, toxicity, etc.:

(i) Schizonticidal drugs for clinical and parasitological cure:

Chloroquine, Amodiaquine, Quinine, Quinidine, Pyrimethamine, Trimethoprim, Proguanil, Sulfonamides in combination with Pyrimethamine, Mefloquine, Halofantrine and Artemisinin.

(ii) Gametocytocidal and anti-relapse drugs:

8-Aminoquinoline group-Primaquine is the only compound having action on gametocytes and hypnozoites.

Note: The current status of drug resistance of malaria parasite to antimalarials is given in Chapter-III, Section-VI on Monitoring of Drug Resistance in *P. falciparum* infection in India.

As regards action of different antimalarials on various stages of malaria parasite of different species, some of the salient points considered by the Committee are :—

I (a) Chloroquine is a very effective and rapidly acting schizonticidal drug. The drug is least toxic with a few adverse effects. Resistance to this drug has been selective in *P. falciparum* in some parts of the country.

(b) Amodiaquine has similar action as Chloroquine but it is more toxic if used over a longer period for chemoprophylaxis. Its advantage over Chloroquine in Chloroquine resistant cases is short lived due to cross-resistance and therefore it is not recommended for use.

II. Sulpha and other Antifoliate drugs when combined potentiate each other's antimalarial actions. They are slowly absorbed and their action on parasite is much slower than Chloroquine. These are recommended for use against Chloroquine resistant *P. falciparum* cases only.

III. Quinine is an effective schizonticidal drug with a short half life and is used extensively orally and in injectable form. Resistance to Quinine in India has not been reported and therefore it should be reserved for complicated cases.

IV. Mefloquine. This drug is not presently marketed in the country but is available in the international market. It is a schizonticidal drug and acts against all species of parasites but has no action on gametocytes and hypnozoites. It is slowly absorbed, action on parasites is slower than any other antimalarials available. Its half life is very long and therefore, resistant strains are selected more quickly than with any other antimalarials. It has got severe toxic effects especially neuro-toxic as such should be used carefully.

V. Halofantrine. Available internationally and not marketed in the country. The drug has got similar action as Mefloquine. The strains resistant to Mefloquine has shown cross-resistance to Halofantrine and vice-versa. The serious disadvantage is that absorption of Halofantrine is very erratic and even with therapeutic doses, serious complications are likely to arise in spite of careful medical supervision.

VI. Artemisinine group of drugs. These drugs have action as schizonticidal drugs. The action is quicker than other antimalarials available so far. Intravenous administration of these compounds is much safer than the intravenous administration of Quinine. They are

comparatively less toxic than other antimalarials if parentrally used. Oral preparations are also available.

The Committee has reviewed the profile of *P. falciparum* resistance to Chloroquine in the country and observed that resistance is widely scattered but in most of the pockets magnitude and degree of resistance is not very high.

After detailed deliberations and considering the present scenario of parasite profile in the country and their resistance to available antimalarials. the committee has observed that:

(a) Chloroquine is still the drug of choice for treatment of all malaria cases in Chloroquine sensitive areas of the country irrespective of the species involved.

(b) 600 mg of Chloroquine-adult dose (10 mg per kg body weight) is adequate to treat *P. vivax* and *p. malariae* infections provided the drug is taken as a single dose, ingested and not vomited.

(c) For treatment of *P. falciparum*, although in most parts of the country 600 mg. adults dose (10 mg per kg body weight) is adequate, but in the areas declared resistant or where the falciparum incidence is very high and in other high risk areas a dose of 1500 mg in three divided doses of 600 mg single dose each on first and second day and 300 mg on the third day (25 mg per kg body weight) over three days in divided doses will cure most of the cases of *P. falciparum*. However, some cases may not respond, which can be presumed to be infected with Chloroquine resistant strain of *P. falciparum*. In these cases Metakelfin or Fansidar can be given (three tablets as adult dose). As on date there is no evidence of resistance to these drugs in the country.

The Committee recommends that:

I. The first line of treatment is Chloroquine and the second line is Sulfalene/Sulfadoxine Pyrimethamine combination. In cases resistant to these two drugs and in severe and complicated malaria cases, Quinine is the drug of choice.

II. All suspected malaria cases should be presumptively administrated 25 mg/kg body weight of Chloroquine base over three days with a single dose of primaquine 0.75 mg/kg body wt. This drug regimen is to be followed up to the subcentre level throughout the country but at present to be limited to the high risk areas. In the low risk areas, Drug Distribution Centre's (DDCs) and Fever Treatment Depots (FTDs) presumptive treatment with (10 mg/kg. body weight) Chloroquine single dose will continue.

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III. The dose of Primaquine for *P. vivax* cases is 0.25 mg/kg body wt. daily for 5 days to prevent relapse and for *P. falciparum* 0.75 mg/kg body wt. single dose for gametocytocidal action.

IV. Amodiaquine has no advantage over Chloroquine in Chloroquine resistant areas considering the toxicity associated with its prolonged use. Amodiaquine may be withdrawn from the programme and also from the private sector.

PRESUMPTIVE TREATMENT IN HIGH RISK AREAS

Chloroquine base	Day 1	10 mg/kg b.w.	(600 mg adult)
Primaquine	Day 2	0.75 mg/kg b.w.	(45 mg adult)
Chloroquine base	Day 3	10 mg/kg b.w.	(600 mg adult)
Chloroquine base	Day 3	5 mg/kg b.w.	(300 mg adult)

RADICAL TREATMENT AFTER MICROSCOPIC CONFIRMATION OF SPECIES: IN

CHLOROQUINE SENSITIVE *P. FALCIPARUM* AREAS

P. vivax — Primaquine 0.25 mg/kg b.w. daily for five days.
P. falciparum — No further treatment is required.

IN CHLOROQUINE RESISTANT *P. FALCIPARUM* AREAS

P. falciparum — Single dose of 25 mg./kg b.w. Sulfalene/Sulfadoxine and 1.25 mg/kg b.w Pyrimethamine (3 tabs Adult) with Primaquine 0.75 mg/kg b.w.

PRESUMPTIVE TREATMENT IN LOW RISK AREAS

Chloroquine base single dose 10 mg/kg b.w. (600 mg adult)

RADICAL TREATMENT AFTER MICROSCOPIC CONFIRMATION OF SPECIES

P. vivax — Chloroquine 10 mg./kg b.w. single dose and Primaquine 0.25 mg/kg b.w. daily for five days.

P. falciparum — Chloroquine 10 mg/kg b.w. plus Primaquine 0.75 mg/kg b.w. single dose.

V. In severe and complicated malaria cases with *P. falciparum* infection (microscopically confirmed), intravenous Quinine is the drug of choice. Intramuscular or intravenous Chloroquine is not well tolerated by children or by pregnant women and therefore may be used very cautiously and only when Quinine is not available.

VI. Although *P. falciparum* cases can be cured with the above drugs provided the treatment is not delayed and supportive, therapy is started in time. The Committee is of the considered view that in the light of the demand made by the medical fraternity Mefloquine can be used for treatment of *P. falciparum* cases resistant to Chloroquine only and not for treatment of *P. vivax* cases. Therefore, it is recommended that the Drug Controller of India may stipulate strict conditions for import, sale and use of Mefloquine through a depot system where:—

(a) It should be mandatory that the drug is issued only on the prescription by a qualified registered medical practitioner.

(b) The prescription should be accompanied by a laboratory report issued by a qualified parasitologist indicating that there are *P. falciparum* rings in the peripheral blood and not gametocytes alone.

VII. Considering the erratic absorption of Halofantrine, its toxic effect even with therapeutic doses and difficulty in management of cases with toxic manifestations, the Committee is of the opinion that this drug should not be introduced in the country. Another further corroborative factor is that *P. falciparum* strains resistant to Mefloquine show cross-resistance to Halofantrine and vice-versa.

VIII. The Committee has observed that sufficient quantity of Quinine injectable is not available in the country to treat the estimated serious cases likely to occur in future. Therefore, the committee is of the view that Artemisinin and its derivative should be introduced for the management of severe and complicated *P. falciparum* infection in the areas of resistant foci.

These drugs should be made available in injectable form only to prevent misuse but agai careful monitoring of the distribution system is imperative.

IX. Quinine will be reserved for use in severe and complicated malaria but will b used in cases not responding to Chloroquine and Sulfa Pyrimethamine combinations. I case of non-availability of Quinine, Quinidine may be used under strict cardiac monitorin

X. Primaquine is the only drug available which acts against the gametocytes o *P. falciparum* as well as hypnozoite of *P. vivax*. The committee feels that this drug should b made available freely in the market on prescription of a physician for radical treatment.

XI. Under the National Anti-Malaria Drug policy, it is recommended that Primaquin may be administered to *P. vivax* cases for five days @ 0.25 mg/kg b.w. daily to prevent relapses. A 14 days radical treatment is not advocated because of toxicity, operational difficulty and also it has very little advantage over five days radical treatment in an endemic area. How- ever, those physicians who want to administer 14 days radical treatment should do so unde close supervision, carefully monitor for the complications which are sometimes very serious with a fair risk of mortality.

Note: Before commencing 14 days treatment with Primaquine, if facilities are available, G6PD estimation should be done or weekly dose of 45 mg may be given for 8 to 10 weeks. However, in endemic areas anti relapse treatment is not mandatory.

XII. **Chemoprophylaxis.** The Committee is of the considered view that population living in non-endemic areas do not require chemoprophylaxis unless they temporarily migrate to endemic areas. The population living in endemic areas except pregnant women should not be put in long-term prophylaxis on account of chronic toxic effects of the drugs.

Pregnant women living in endemic and hyper-endemic areas are highly vulnerable to complications of *P. falciparum* because of suppressed immunity. Chemoprophylaxis is therefore recommended and should commence at the end of first trimester of pregnancy.

Travellers including service personnel who temporarily go on duty to meso-endemic or hyperendemic areas are also at high risk and therefore must be on chemoprophylaxis starting before the transmission period and terminating four weeks after the transmission period is over.

The temporary labour population migrating from other parts of the country to meso-endemic and hyper-endemic areas are also at high risk and should be under chemoprophylaxis. Considering that there is poor compliance from this group, the Committee suggests that after initial screening and radical treatment at the point of entry, it is better to put them under weekly case detection and treatment on technical grounds.

The Committee then has considered the suitability of different antimalarials available for chemoprophylaxis and recommends that Chloroquine is the drug of choice for Chemoprophylaxis. After a loading dose of 10 mg/kg b.w. it should be followed by a weekly dose of 5 mg/kg b.w. This is to be continued till one month after delivery in case of pregnancy or stay in an endemic area. Chemoprophylaxis with Chloroquine is not recommended beyond three years because of its cumulative toxicity. In Chloroquine resistant areas chemoprophylaxis is recommended with Chloroquine 5 mg/kg b.w. weekly and Proguanil 100 mg. daily.

Amodiaquine and Sulfa-Pyrimethamine combination are not recommended for prophylaxis due to the toxic effects on prolonged use.

Mefloquine and Halofantrine are not considered suitable for chemoprophylaxis due to their toxic effects and also since *P. falciparum* resistance problem is not very serious in the country.

Quinine and Artemisinin group of drugs are not suitable on account of very short half life and consequently require repeated administration of drugs.

XIII. The Committee has deliberated on the use of Ayurvedic and Homeopathic preparations for treatment of malaria. In the Ayurvedic system Ayush-64 and other similar combinations have been found to be effective against the human Plasmodium. However, their treatments regimen is prolonged and has no advantage over Chloroquine/Sulpha-Pyrimethamine combinations. Also several homeopathic drugs are reported to be effective against malaria but need to be scientifically investigated. The committee strongly recommends that modern chemotherapeutic antimalarials are never to be used in combination with Ayurvedic or Homeopathy drugs because their compatibility with such drugs has not been investigated so far.

XIV. Monitoring of drug resistance, Clinically and parasitologically, should also be conducted by the state government and the existing *P. falciparum* monitoring teams of NAMP would be responsible for independent monitoring in selected areas. Monitoring would be taken by NAMP/MRC.

XV. Research institutions and medical colleges should be involved in the developme of malaria diagnostics, screening and testing of newer drugs, estimation of parasite sensitivi etc. so that the national programme is updated and new technologies can be incorporated the control strategy.

XVI. To facilitate easy availability and to overcome the problem of antimalari shortage, it is recommended that the Government of India should develop and promote dru availability in remote areas through the private sector. The State governments should als establish a system to monitor availability of drugs in the periphery.

XVII. Quality control of drugs should be organized and strictly implemented to ensu proper distribution of standard drugs. The state health authorities will be requested b NAMP to carry out sample checks on drugs supplied through State Drug Controller.

XVIII. Government of India should initiate steps to encourage indigenous productio of cinchona and Artemesia Annua. An inter ministerial group may be setup to sugge measures for production in the public as well as private sector.

XIX. Health education on the prevention and treatment of malaria should be a part o NAMP activity. Active involvement of CHEB should also be ensured. It is essential tha wide publicity be given to the revised antimalaria drug policy and educate the medica and paramedical professionals in the private and public sectors through Indian Medica Association.

XX. All antimalarial drug packaging should carry complete information in Englis Hindi and other regional languages on the dosage, side effects, antidotes, date of manufactur Date of expiry and other information such as on "for complete cure Primaquine therapy necessary except in infants and pregnant women".

XXI. The medical practitioners should follow established guidelines but in case o non-response they are at liberty to administer other antimalarials and in combination wit antibiotics as considered best.

XXII. Malaria drug policy should be reviewed atleast every two years. This is imp rative in view of the rapidly changing epidemiological Scenario of malaria, drug resistan in *P. falciparum* and perhaps in *P. vivax*, new antimalarials and availability of more info mation on existing drugs.

INSTRUCTIONS ISSUED BY DIRECTORATE OF NAMP—TO PERIPHERAL WORKERS ON THE USE OF ANTIMALARIALS

Presumptive Treatment

The presumptive treatment is given to all fever cases or cases with history of fever for the past 15 days, in such cases the blood smear is collected immediately.

The presumptive treatment is given to all persons irrespective of age or sex. Even pregnant women in any month of pregnancy or during postpartum period. It should also be administered to fever cases of DDCs, etc.

All FTD/DDC holders, MLVs MPWs (Male/Female), Health Supervisor (Male/Female), Laboratory Technicians and PCD are authorised to give presumptive treatment.

(a) Presumptive treatment in low risk areas comprise of a single dose of Chloroquine Phosphate @ 10 mg/kg b.w.

ADULT DOSE

- A SINGLE DOSE OF CHLOROQUINE PHOSPHATE-600 mg. (4 Tablets)
- ADMINISTERED BY ALL AGENCIES

Table 3.3: The age-wise dosage of Chloroquine for presumptive treatment @ 10mg/kg. body weight

Age in Years	mg base	No. of Tablets
<1	75	1/2
1-4	150	1
5-8	300	2
9-14	450	3
15 and above	600	4

(b) (i) Presumptive treatment in high risk areas up to the subcentral level is as follows:—

25 mg/kg. b.w. of Chloroquine base over three days (10 mg/kg. b.w. each on first a second day and 5 mg/kg. b.w. on third day) along with a single dose of Primaquine 0.75 m per kg. b.w. on the first day. This drug regimen is to be followed up to the subcentre level in high risk areas of the country identified as per criteria laid down by the Expert Committee 1995.

Table 3.4: The age-wise dosage

Age in years	First day		Second day	Third day
	Chloroquine	Primaquine	Chloroquine	Chloroquine
	mg base	mg base	mg base	mg base
<1	75	nil	75	37.5
1-4	150	7.5	150	75.0
5-8	300	15.0	300	150.0
9-14	450	30.0	450	225.0
15 & above	600	45.0	600	300.0

Note: Pregnant women and infants are not to be given Primaquine.

(b) (ii) Presumptive treatment in high risk areas by DDCs, FTDs and MLVs:

The FTD and DDC holder as well as MLVs will administer 10 mg/kg. b.w. of Chloroqui base in a single dose without Primaquine as is followed in the low risk areas.

(c) The presumptive treatment in areas with *P. falciparum* resistant strains where modified 1995 Drug Policy of NAMP at different levels is implemented will be as under:

Table 3.5: Presumptive Treatment in *P. falciparum* Resistant Areas

Adult Dose

S.No.	Agency	Presumptive Treatment	
		Drug	Dose
1.	DDCs, FTDs & MLVs	Chloroquine	600 mg as a single dose
2.	ACD MPW (Male & Female) Health Supervisor (M&F)	Chloroquine + Primaquine	1500 mg in 3 divided daily doses i.e. 600 mg each on 1st and 2nd day & 300 mg on 3rd day with a single dose 45 mg Primaquine on 1st day
3.	PCD* PHC Medical Officer OPD	Sulphalene/ Sulphadoxine + Pyrimethamine	1500 mg + 75 mg as a single dose

*In case microscopic diagnosis is not available immediately at a PCD, the presumptive treatment should be Chloroquine plus Sulpha combination because Sulpha combination has very little action on *P. vivax*. However, the person administering the presumptive treatment should ensure that Sulpha combination tablets are swallowed in his presence and he will advise the patient to consume Chloroquine tablets soon after.

Note: Considering that Amodiaquine has no advantage over Chloroquine in the treatment of *P. falciparum* and also the toxicity associated with this drug on prolonged administration, it has been withdrawn from NAMP.

RADICAL TREATMENT

All microscopically positive cases of malaria should be given radical treatment wit Primaquine for its gametocytocidal and anti-relapse properties. This ensures a complete cu from malaria in a positive case, and makes the patient non-infective to mosquitoes. Howeve in high risk areas, the fever cases has to be given three days presumptive treatment i.e. 150 mg Chloroquine and 45 mg Primaquine (adult dose), and later if found positive for *P. falc parum* need not be given radical treatment.

(a) **Radical treatment for** *P. vivax*, *P. malariae* **and mixed infections:**

The adult dose/drug schedule is as under:—

A single dose of 600 mg Chloroquine (10 mg/kg. body weight) and 15 mg Primaquin (0.25 mg/kg. body weight) on the first day followed by 15 mg Primaquine (0.25 mg/kg. bod weight) daily for the next four days:

Table 3.6: The age-wise Dosage of Radical Treatment

Age in years	Tablet Chloroquine		Tablet Primaquine	
	Mg base single dose	No. of tablets (150 mg)	Mg based Daily dose for 5 days	No. of tablets (2.5 mg)
< 1	75	2	nil	nil
1-4	150	1	2.5	1
5-8	300	2	5.0	2
9-14	450	3	10.0	4
15 >	600	4	15.0	6

In high risk areas where presumptive treatment with 1500 mg Chloroquine has been given and the patient is found positive for *P. vivax* another dose of Chloroquine-600 mg need not be administered but five days schedule of Primaquine must be given.

(b) Radical Treatment for *P. falciparum* Infection:

If the load of malaria positive cases is very high in an area with *P. falciparum* who were given a single dose of Presumptive Treatment with 600 mg Chloroquine (i.e. 10 mg/kg. b.w.) they should be given full radical treatment on priority.

The Adult dose is :

1500 mg Chloroquine in three divided/daily doses (i.e. 600 mg each on first and second day & 300 mg on third day) plus 45 mg Primaquine on first day.

This dose is to be suitably adjusted for other age groups also.

Caution : INFANTS AND PREGNANT WOMEN ARE NOT TO BE GIVEN PRIMAQUINE

(c) The radical treatment of cases in chloroquine resistant strain areas for *P. falciparum* as suggested under the revised Drug Policy is as follows:--

Adult dose

Sulphalene/sulfadoxine—1500 mg

\+ Single Dose

Pyrimethamine 75 mg

(3 tablets)

Thereafter

Primaquine 45 mg Single dose

These drugs should be given cautiously and not on the same day as they are known t precipitate haemolytic crisis in sensitive cases with G6PD deficiency. The drug administrato should ensure that the patient swallows Sulpha combination tablets in his presence and the patien is given clear instructions to consume Primaquine tablets on the following day withou fail.

Table-3.7: The Age-wise Dosage

Age in Years	Sulphalene/sulphadoxine + Pyrimethamine		Primaquine	
	mg base	No. of tablets (500 mg + 25 mg)	mg base	No. of tablets (15 mg)
1	2	3	4	5
>1	125 mg + 6.25 mg	4	nil	nil
1-4	500 mg + 25 mg	1	7.5 mg	2
5-8	750 mg + 37.5 mg	1	15 mg	1
9-14	1000 mg + 50 mg	2	30.0 mg	2
15 & above	1500 mg + 75 mg	3	45.0 mg	3

In cases resistant to above drugs, and in severe and complicated malaria cases and *P. falciparum* infections (microscopically confirmed) I.V. Quinine is given as per schedule given below :—

Dosage of Quinine dihydrochloride I.V.

Quinine 10 mg/per kg b.w. thrice daily as intravenous infusion in 5% dextrose/glucose solution over 4 hours.

When patient regains consciousness, same dosage schedule of quinine is given orally to complete seven days treatment.

However, the radical treatment for *P. vivax* will remain the same i.e. Chloroquine @ 0.25 mg/kg. b.w. daily for first day to fifth day.

Use of New Antimalarials by Registered Medical Specialist

1. Mefloquine can be used only for treatment of *P. falciparum* cases resistant to Chloroquine and not for *P. vivax* cases but it should be mandatory that Mefloquine is issued only on the prescription by a qualified registered medical specialist and the prescription is supported by laboratory report issued by a qualified Parasitologist indicating that there are *P. falciparum* rings (and not gametocytes alone) in the peripheral blood smear.

2. Artemisinin and its derivatives can be used in the management of severe and complicated *P. falciparum* infection in areas of resistant foci. The drug is to be made available in injectable form to prevent its misuse and careful monitoring of its distribution is imperative.

CHEMOPROPHYLAXIS

No true chemoprophylactic drug is available which acts directly on 'sporozoites' and prevent establishment of malaria infection in man (absolute prophylaxis). All antimalarials which are used for clinical chemoprophylaxis are schizonticidal drugs which do not prevent malaria infection but suppress appearance of clinical symptoms by acting on erythrocytic stages. Therefore, a good suppressive drug should have the following qualities:

(a) It should be fast acting against Erythrocytic stages.

(b) It should have long half life so that frequent drug administration is not necessary.

(c) It should not be toxic in the dosage required for suppressive treatment over prolonged period.

Drawbacks :

1. At present no such drug is available although 4-Aminoquinolines are fast acting and safe enough. The sulpha group with pyrimethamine combination is quite effective but not safe since on prolonged use it has toxic effects. People who are allergic to sulpha drugs may develop skin lesions or ganulocytosis which at times may be fatal. The 4-Aminoquinoline group of drugs produce skin reactions and permanent changes in the eye like neuro retinitis if taken continuously for a number of years. Quinine is not suitable as it is to be administered more frequently and toxicity much more.

2. The other drawback is that continuous uninterrupted drug compliance over a prolonged period during transmission period cannot be ensured.

3. Discontinuation of treatment leads to break through which may go untreated for a long time.

4. If the drug schedule is not strictly followed, chances of developing a resistant strain to *P. falciparum* in the area becomes more.

Therefore, the suppressive treatment or chemoprophylaxis is not recommended for those who are permanent residents of meso or hyperendemic areas.

Most appropriate groups who will be benefited by the chemoprophylaxis are:--

(a) Tourists/travellers from non-malarious areas to malarious areas.

(b) Military or Paramilitary groups moving into malarious areas.

Caution: The chemoprophylaxis or suppressive treatment should be started a week before departure and not to be terminated immediately after leaving the malarious area and should be continued for at least 4 weeks even if the person becomes afebrile and is negative for Malaria Parasite.

Chemoprophylaxis should be terminated with radical treatment schedule of five days at the recommended dosage.

(c) Pregnant women in endemic and hyperendemic areas.- Chemoprophylaxis to be started after first trimester of pregnancy and continued for one month after the child birth. However, before the commencement of chemoprophylaxis, if a pregnant woman is foud positive, full course of Chloroquine is to be given. In the event of breakthrough during chemoprophylaxis, investigate drug compliance and administer full treatment with second line of drug.

Note: In the postnatal period at the time of termination of chemoprophylaxis, the Hb level should be estimated. If a woman is still anaemic (Hb below 7 gm), the chemoprophylaxis should be continued along with treatment for anaemia. Chemoprophylaxis can be discontinued and Radical Treatment for five days duration, when anaemia has been corrected.

1. The drug of choice for chemoprophylaxis in:

(a) Chloroquine Sensitive Areas

Chloroquine	Dosage schedule 10mg/kg. b.w. as loading dose and thereafter 5. mg/kg b.w. at weekly intervals, not recommended beyond three years because of cumulative toxicity.

(b) Chloroquine Resistant Areas

*Chloroquine	5mg/kg b.w. at weekly interval
+	(300 mg-adult dose)

Proguanil	1.5 mg/kg b.w. daily (100 mg-adult dose)

*Notes : 1. Since Proguanil is to be taken daily drug compliance is poor.

2. Amodiaquine is not recommended for chemoprophylaxis since prolonged use of this drug produces serious toxic manifestations. Death rate due to toxic effects of Amodiaquine is more than the risk of death due to severe malaria infection. Therefore, Amodiaquine has now been withdrawn from the programme.

PART-B

SECTION-I

CLINICAL MALARIA—DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

Introduction

The clinical picture of malaria, its differential diagnosis, management of uncomplicated and complicated cases have been extensively dealt with in different text books of medicine. A large number of monograms on this subject have been published by WHO and Directorate of NAMP. In this chapter, the subject has been dealt with keeping in view the limitations usually encountered in the field operations of malaria control programme. The epidemiological status of the locality modifies the clinical picture of malaria case(s). The clinical picture shows wide variations in different malaria paradigms. The management of malaria cases at different levels of health delivery system has its own drawbacks because sometimes essential facilities are not available at the primary, secondary and even tertiary referral centres of health care system. The medical specialists at different levels are sometimes not aware of the latest developments in malaria chemotherapy and case management. An attempt has been made in this chapter to provide some clinical information on the subject.

Malaria was called as the king of diseases by Charaka and Susruta, the great Indian physicians of Ayurveda. It is an apt description of the disease as malaria infection produces clinical symptoms of diverse nature and can mimic many other diseases. To understand the course of clinical events in a malaria case, its clinical pathology should be properly understood.

Incubation period in human host varies with species of malaria parasite infecting a person. The incubation period is described as lapse of period between introduction of sporozoites in the body and appearance of clinical symptoms. The sporozoites enter the cells within half an hour of inoculation and develop in the hepatocytes. The incubation period is usually from 9 to 28 days. It is shortest for *P. falciparum* and longest for *P. malariae*.

P. falciparum ..... Average incubation period is 12 days, range being 9-14 days.

P. vivax ..... Average incubation period is 15 days, range being 12 to 17 days. Some *P. vivax* strains show a much longer incubation period i.e. up to 6-12 months.

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P. malariae ..... Incubation period is 28 days, range being 18 to 40 days or even more.

After completion of pre-erythrocytic cycle, the merozoites are liberated from liver in the peripheral circulatory system. These menozoites then infect the RBCs. In non-immune cases, prodromal symptoms are presented. During this stage the malaria parasite may not be microscopically demonstrated in the peripheral blood.

Pre-patent period

The period between inoculation of sporozoites and demonstrable parasitaemia in the peripheral blood is pre-patent period.

Clinical Course of paroxysm in Uncomplicated Malaria

Cold Stage

The clinical symptoms of malaria start with shivering (rigor). During this stage the shivering may range from the feeling of chill to uncontrollable shivering with intense cold which is not relieved even if the patient covers himself with clothings and blankets. This period lasts for 1/2 an hour to 2 hours. During this period, the pulse is rapid but weak, lips and fingers may show cyanosis, skin is usually dry and pale. vomiting may occur in some cases especially children.

Hot Stage

The cold stage is immediately followed by hot stage. The intense cold gives way to distressing heat. The patient usually throws away the covering clothes. Temperature sometimes may rise up to 41°C (106°F). During this priod, skin is dry, and burning sensation, intense headache, nausea and vomiting are common. There may be visual disturbances like diplopia, photophobia, disorientation and convulsions especially in young children. The temperature lasts for a period of 8 to 12 hours.

Sweating Stage

The temperature comes down by crisis often below normal levels with profuse sweating. This stage is called the sweating stage. The patient is exhausted and sometimes goes in to deep sleep. The sweating stage may last from 2 to 4 hours.

Fever Free Period

After the fever episode, the patient may have a fever free period. Periodicity of fever episode is 36 to 48 hours in case of *P. falciparum* and 48 hours in *P. vivax* and in *P. malariae* it is 72 hours.

Periodicity of fever :

In the initial stage of malaria infection intermittent periodicity of fever may be absent or in cases where more than one brood of liver merozoites are liberated in blood circulation immediately one after the other. Gradually after 2 to 3 bouts of fever, the periodicity is more or less well established.

Therefore, in the beginning, the fever episode accompanied with intense headache, fatigue, nausea, muscular pains is more often mistaken for influenza or other bacterial or viral infections.

The above picture is presented by an uncomplicated case of malaria, usually *P. vivax* and *P. malariae* and quite often by *P. falciparum*.

Clinical presentation in children

In children, the clinical symptoms may be accompanied with convulsions and disorientation which may be attributed to hyperpyrexia. The pyrexia is usually very high.

The clinical picture in case of *P. falciparum* shows lot of variations. Very often these variations depend on a large number of factors including the number of sporozoites inoculated, the immune status of the individual and most probably *P. falciparum* strains infecting the individual.

Clinical Pathology

To understand the further course of clinical manifestations in malaria patients, it is necessary to review the clinical pathology of malaria infection. The invasion of red blood cells by merozoites of malaria infection. The sectors which determine the course of reaction of the host to parasite invasion are governed by :—

(i) Action of Plasmodia or its metabolic products on RBC's

(ii) General changes in blood flow related to pyrexia and altered Biochemistry of the body

(iii) Local changes due to damage to endothelial cells of the blood vessels caused by parasitic products

(iv) Tissue toxaemia resulting from the metabolic products of the plasmodia

(v) Tissue anoxia due to decrease in oxygen carrying capacity of the blood and changes in the capillary endothelium.

Changes in RBC's

When the malaria parasite enters the RBC's it produces some morphological changes in it. In case of *P. vivax* RBC's are enlarged and in case of *P. falciparum* knob like structure appear on the cell wall of RBC's. These have been clearly observed under electron microscope. How and why these knobs appear is not yet fully understood. It has been thought that these knob like structures produce cyto-adherence in RBC's infected with *P. falciparum*. These RBCs adhere to (i) each other, (ii) to normal RBCs and also (iii) to the walls of the capillaries. It has been thought that some of the biochemical products of parasite metabolism which are toxic in nature, produce damage to the endothelial cells of the capillaries and are more permeable to fluids. In some instances they allow transmigration of white blood cells into the surrounding areas.

The cyto-adherence of parasite results in blockage of capillaries and retards the flow of blood in the area resulting in anoxemia of the surrounding tissues. All aspects of the process of altered biochemistry of human body during malaria infection are not very clearly understood.

Pathogenesis of fever in man is supposed to be the response of human body to toxic products of the infecting agent or indigenous products from destroyed RBCs. On the other hand, it may be the interaction of specialised receptors on thermo sensitive centres of hypothalamus, resulting in release of some chemicals stimulating vaso-constriction of peripheral vessels, decreasing the heat loss with resultant hyperthermia. However, the body response as witnessed during cold stage prior to hyperpyrexia may be a part of human reaction akin to other allergic reactions triggered by parasite toxins and RBC's debris released at the time of liberation of merozoites since the cold stage starts immediately after the release of merozoites in the peripheral blood.

Most of the other manifestations in *P. falciparum* malaria develop from one simple pathology of cyto-adherence to RBCs. In whichever part of the internal organ the flow of blood is

restricted due to the cyto-adherence and damage to capillary endothelium, the symptoms related to the organ concerned are manifested such as cerebral symptoms, symptoms of congestion of gastro or respiratory organs i.e. lungs and intestinal system. Some of the symptoms may be due to restriction of blood flow through the endocranial glands. The nephrotic symptoms are due to RBCs in *P. falciparum* malaria where the parasitised RBCs are destroyed as well as some of the normal RBCs are also haemolysed, producing severe anaemia during the course of a fever episode. Even in patients having moderate peripheral parasitaemia, with each bout of fever 0.5 gm of haemoglobin is lost from peripheral circulation. Thus repeated bouts of fever, produce sudden fall in haemoglobin and reduce oxygen carrying capacity of blood to the levels which result in hypoxia of the tissues. There is rise in billirubin in plasma and urine directly or indirectly depending on quantum of destruction of RBCs per fever bout and liver damage. There is also excretion of albumin in urine along with red blood cells, hyaline and granular casts when acute renal dysfunction develops.

The spleen is enlarged due to the fact that reticulo-endothelial system has to cope up with a very large amount of RBC's debris and other products of parasite. In the initial stages spleen is just palpable on deep breathing and is tender. Therefore, it is clear that clinico-pathological picture of malaria infection which arises out of simple invasion of RBCs by malaria parasite becomes very complex. As the disease progresses, the pathological process in different organs once initiated continues till the parasitaemia is controlled.

Anaemia and Bone Marrow Depression

Anaemia is most pronounced in malaria infection. It is quite severe in case of untreated acute *P. falciparum* infections. Severe anaemia is also encountered in untreated long standing *P. vivax* cases. The blood picture is adversely affected during malaria infection due to depression of haemopoetic system including bone marrow. However, severe anaemia is rarely the cause of death in malaria even in *P. falciparum* cases. Recovery of haemopoetic system is often slow, despite parasitic cure. Sometimes it may be due to the effect of chemotheopeutic drugs used for treatment of malaria, like Pyrimethamine which produces delayed recovery from anaemia. The bone marrow response to malaria infection is normoblastic and monocytic generally with well marked erythroplastic hyperplasia. During malaria infection in pregnancy, severe anaemia is noticed in endemic areas. If the infection is not treated well in time, it may lead to increased mortality. In *P. falciparum* malaria, anaemia coupled with concentration of parasites in placenta produces hypoxia of foetus leading to foetal distress and abortion. This is quite common and serious in primiparous women especially in poor sections of the society who commonly suffer from low haemoglobin concentration.

Intravascular Coagulation and Bleeding Tendency in *P. Falciparum* Malaria

Intravascular coagulation is relatively rare and occurs late during the sickness. The is some evidence of reduced capability of clotting due to decrease in plasma coagulation fa tors and reduced platelet concentration. Platelets are probably entrapped in the spleen. Ha mostatic alteration sometimes include low plasma fibrinogen level, decreased platelet cou resulting in haemorrhages. In late stages disseminated intravascular coagulation develops association with thrombocytopaenia, fibrinogenopaenia and low levels of other coagulation fa tors thus leading to increased mortality and morbidity of severe *P. falciparum* cases.

Cardiac lesions

In severe cases, there are petechial haemorrhages in the pericardium and capillaries ar sometimes full of numerous parasitised cells. The phenomenon may lead to degenerativ changes in the cardiac muscle fibres, sometimes myocardial infection has also been reported Among the other circulatory signs, drop in blood pressure may be seen. In stages of shock the blood pressure falls drastically and pulse rate reaches 150 per minute or above and is hardl perceptible. Peripheral vascular resistance is decreased because of orthostatic hypotension Blood circulation in skeletal muscles is disturbed. There is loss of vascular tone in patients wit low blood pressure especially just after a severe febrile attack.

Most of these clinico-pathological changes are reversible, unless parasitaemia is allowe to continue unaffected in the host. In the long run some of the organs are irreversibly damaged The internal factors which modify the human response to malaria infection are humoral an cellular responses of the immune system as well as the nutritional status of the host.

Clinical Diagnosis of Malaria Paroxysm

It is not difficult to clinically diagnose a case presenting classical symptoms of malari ie., chills/shivering followed by hyperpyrexia which resolves by crisis with profuse sweating Fever invariably comes with typical periodicity. If associated with spleenic enlargement an anaemia, which are usually encountered in chronic cases, clinical diagnosis of malaria is almos certain and laboratory confirmation is a mere formality.

HOWEVER ALL MALARIA PATIENTS DO NOT SHOW TYPICAL SIGNS AND SYMPTOMS AS MENTIONED ABOVE. MALARIA SYMPTOMS ARE MODIFIED BY THE IMMUNE STATUS, AGE, SEX, PREGNANCY AND PRESENCE OF ANY OTHER CONCOMITANT DISEASE.

SALIENT FEATURES OF MALARIA—DIFFERENT SPECIES

Species	Severity of Signs and Symptoms	Duration of Single Infection	Periodicity of Fever	Complications
P. falciparum	MODERATE TO SEVERE	1 TO 2 YRS	DAILY OR ALTERNATE DAY	- HYPERPYREXIA - ANAEMIA - RENAL HEPATIC, INTESTINAL - CEREBRAL MALARIA - SHOCK, COLLAPSE - FATALITY
P. vivax	MILD TO MODERATE	3 TO 4 YRS	ALTERNATE DAY (BENIGN TERTIAN)	- ANAEMIA - EMACIATION - SPLEENOMEGALY - HEPATOMEGALY

CLINICAL PICTURE AND DIFFERENTIAL DIAGNOSIS OF UNCOMPLICATED MALARIA

(1) **History taking** — Physician should elicit detailed history of fever episode and presenting signs and symptoms

(2) **History of movement** — History of exposure to malaria is quite important. Enquire if the patient has recently been travelling—where, when and for how long strongly suspect malaria amongst those who have fever, aneamia enlarged Tender spleen and who are from a malarious area or have recently visited a malarious area.

(3) **History of recent blood transfusion** — The physician should not forget to enquire history of recent blood transfusion from a fever case both ambulatory or indoor. The incubation period of malaria varies from case to case. The incubation period and severity of symptoms are also governed by the malaria immunity of individual developed during previous exposure to malaria in *P. vivax*. Successful invasion and fever manifestation occur even if 10 parasites are injected during blood transfusion. The incubation period is usually 12 to 17 days.

I. *P. VIVAX* INFECTION

A. *Clinical features*

(a) Cold stage

Patient gets a chilly sensation or uncontrollable shivering (rigor) lasting about 1/2 to 2 hours followed by rise in temperature.

(b) Hot stage—fever episode

- The fever may last for 8 to 10 hours
- may occur daily or in a well developed classical case on alternate days (Benign Tertian malaria)
- Temperature may range upto 104° F and above
- during fever stage, headache, bodyache and vomiting occurs.

(c) Remission of fever—sweating stage

- The fever comes down by crisis after profuse sweating
- after remission of fever patient feels weak but relieved
- other symptoms also disappear

d) Other signs and symptoms

- after about 3-6 paroxysms the spleen is palpable
- liver is just palpable and tender in few cases
- relapses occur in three to five years even without treatment
- the clinical course of the disease is mild, periodicity is well established even in the initial stages.
- infants and young children with hyperperexia may show disorientation and convulsions. Because of the above, clinical condition is misleading, the patient may be misdiagnosed as suffering from *P. falciparum* infection or some other ailment involving central nervous system.

THEREFORE, TO ARRIVE AT A FINAL DIAGNOSIS THE CORRECT SPECIES IDENTIFICATION BY MICROSCOPY ASSUMES GREATER IMPORTANCE IN CASE OF INFANTS AND CHILDREN.

DIFFERENTIAL DIAGNOSIS

1. Septic conditions

(a) Acute suppurative otitis media

(b) Abscess/Cellulitis

If there is daily rise of temperature in the afternoon, malaria is suspected and in evening rise there is a strong suspicion of septic condition.

2. Viral diseases

(a) Infective hepatitis

- fever with jaundice
- Van Den Bergh reaction
- Direct

(b) Dengue

- Severe generalised muscular pains, saddle back, seven days fever curve, slow pulse, lymphadenitis and rash.
- Marked leucopaenia, decreased platelets in children and no spleenomegaly.

(c) Sand fly fever

- Severe orbital pain, conjuctival injection intense, photophobia, three to four days continuous fever.

- Relative and absolute diminution in neutrophils with relative increase an absolute increase in immature neutrophils (also in Dengue)

- No spleenomegaly, subjective complaints of melancholia and apathy may persis after Dengue or in sand fly fever but usually not after malaria attack.

(d) Yellow fever

- History of patient suggests visit to yellow fever area in recent past.

- No spleenomegaly

- Pulse stationary with rising or falling temperature

- Intense Jaundice on third day progressive, in nature

- Typical mucoid and black vomit usually on fourth day.

3. Bacterial Diseases

(a) Typhoid fever

- Blood culture positive during first ten days of fever

- Stool culture positive after tenth day with increasing frequency up to fourth or fifth week in diagnostic.

- Typical temperature chart

(b) Relapsing fever

- Sudden onset with spleenomegaly and leucocytosis

- Blood films reveal causative organism of relapsing fever

- Typical relapsing fever curve and lack of response to antimalarial drugs.

(c) Meningococcal infection

- Signs of meningeal irritation

- CSF slightly turbid

(d) Upper respiratory and urinary tract infection symptoms related to the systen involved.

4. Helminthic disease

(a) Early filariasis

- Lymphadenitis with fever.
- Involvement of genitalia in chronic cases. Some acute cases show epididymo-orchitis.
- Leucocytosis and eosinophilia
- Spleenomegaly and anaemia are not present even in the longstanding patients.
- Peripheral blood smear reveals microfilaria

(b) Schistosomiasis

- In early stage fever may be intermittant or quotidian
- History of exposure may be elicited or suspected in cases reporting from endemic areas
- Rash is typical
- Eosinophilia very high
- Serological tests may assist in diagnosis.

5. Protozoal diseases

(a) Kala-Azar

- Spleen enlargement spongy or hard, bleeding gums, notable cachexia, extreme weakness, emaciation
- Fever is continuous
- Early and pronounced leucopoenia
- Blood film, bone marrow, lymph node aspirate may reveal *Leishmania donovoni*

(b) Amoebic Abscess of liver

- low grade fever
- Hepatomegaly liver is tender
- Rigidity of right rectus muscle.
- High leucocytosis with relatively high polymorph count and no increase in monocytes

- Indirect haemoglutination test for amoeba is the specified test
- X-ray /screening chest for liver abscess is helpful

(c) Trypanosomiasis

- Identification of Trypanosoma in blood, lymph node and CSF is diagnostic
- Complement fixation test is also confirmatory
- Mono Nuclear cells and Proteins are raised in the CSF

II. *P. MALARIAE* INFECTION

- Mild clinical manifestations fever has a periodicity of four days (quartan malaria)
- Patient may have parasite in peripheral blood without fever. Untreated infection may last up to 30 years
- Nephrosis has been reported in few cases

III. *P. FALCIPARUM* INFECTION

A. Clinical picture

- Sequence of events in fever episode is similar to that of *P. vivax*.
- Unlike *P. vivax* Infection, usually there is no feeling of well being after paroxysm
- Fever is often high, irregular, intermittent, remittent or continuous type
- Headache and vomiting more common
- Sweating is not a persistent feature
- In hyper/holoendemic areas prolonged low grade parasitaemia of *p. falciparum* infection may result in gradual personality and psychological changes due to permanent damage to brain tissues
- Mortality in patients after development of complications may range from 20 to 50% depending on time lag between the onset of disease and start of specific treatment.

B. Differential Diagnosis General consideration

Some important but general considerations for differential diagnosis are:

1. Sporadic

In time and space usually a single case is reported from a locality or a village. This is true except for an area having fulminating epidemic of *P. falciparum* when a larger number of severe cases may be encountered.

2. Locality

The case is reported from an area known to be endemic for malaria. However, at times a person hailing from a non-endemic area may develop serious complications just after return from malarious area.

3. Transmission

The case usually occurs during malaria transmission season although it can be encountered at any time during the year but during non-transmission season it is very low.

4. Age

No age group is exempted, however, incidence is higher in non-immune infants and children.

5. Sex

Both sexes are equally vulnerable but pregnant women are prone to severe complications.

6. Suppressive Chemotherapy

After discontinuation of suppressive treatment (chemoprophylaxis) severe *P. falciparum* complications can occur within three weeks.

7. At any given time unusually large number of cases with symptoms showing massive and severe involvement of brain, intestines or any other internal organ from the same locality require careful differential diagnosis.

C. Complication of *P. falciparum* malaria

It has been estimated that 0.5 to 2% cases of *P. falciparum* in non-immune population may develop serious complications.

The direct complications due to *P. Faiciparum* infection are mentioned as under in order of frequency of presentations:

1. Hyperthermia
2. Anaemia
3. Hypoglycaemia
4. Dehydration
5. Pulmonary oedema
6. Cerebral malaria
7. Shock-general collapse algid malaria
8. Gastro intestinal manifestations
9. Acute renal failure
10. Haemolytic jaundice-liver damage
11. Black water fever, Haemoglobinuria
12. Petechial Haemorrhages/intravascular coagulation

Any of the above complications can occur in a patient(s) with lowered resistance/ immune status and should be suspected:

(1) In an unexplained fever
(2) Pregnant women
(3) After child birth in post partum period
(4) Accidents
(5) Post operative period
(6) Malnutrition
(7) In association with acute or chronic infections and
(8) Blood transfusion

1. CEREBRAL MALARIA

Clinical signs are similar to those of a diffuse symmetrical encephalopathy:

1. Staring look, no photophobia

2. Dysconjugate gaze

3. Oculogyric crisis

4. Deep stertorous breathing combined with decorticate rigidity can be a part of malaria syndrome. Some times this could also occur on account of hypoglycaemia

5. Neck rigidity does not occur but mild stiffness of neck may be there

6. There are no signs of raised intracranial pressure and the CSF is clear

7. Reflexes : abdominal reflexes are invariably absent and planter responses are usually of extensor type

8. Retinal haemorrhages may be encountered in a few cases

9. Cerebral dysfunction, mental aberration, impaired consciousness, delirium may be there.

MALARIA SHOULD BE FIRST SUSPECTED IN ANY UNEXPLAINED FEVER IN AN ENDEMIC AREA, OR IN A PERSON COMING FROM AN ENDEMIC AREA

Deferential diagnosis

The patient with hyperpyrexia may go in a comatosed condition or may develop coma soon after admission. Coma is often unarousable. A physician should consider other causes of cerebral episode. While arriving at the final diagnosis, in all cases hypoglycaemic coma should also be ruled out.

(i) **Heat Stroke :**

- Generally occurs in summer season
- History of exposure to heat is there
- Hyperapyrexia
- Dehydration with dry and warm skin
- Pronounced typical absence of sweating

During peak summer season with low humidity cerebral malaria is a rare occurrence while heat stroke is more common

The laboratory tests such as blood smear and CSF examination will be normal.

(ii) **Meningitis :**

- Neck rigidity
- Gradual onset of symptoms and progressive deterioration
- History of possible infection
- There may be several such cases from the same locality at the time of epidemic
- Typical neck rigidity is accompanied with changes in CSF findings
- Meningo Coccal meningitis usually occurs in winter season
- Confirmation by CSF examination and blood culture

(iii) **Viral Encephalitis :**

- Occurs in epidemic form
- Several cases with similar history and symptoms come from an area within a short span of time
- Fever, neck rigidity with typical headache and altered sensorium is there
- Usually the cases occur in post monsoon season when cerebral malaria also occurs
- Confirm by TLC/DLC/CSF examination and if possible by isolation of virus

(iv) **Cerebro-Vascular Episode :**

- Origin sudden
- History of long standing hypertension
- Indications of localised involvement of brain due to haemorrhage or thrombosis
- Neck rigidity may or may not be there
- Isolated cases occur in locality
- Cases can occur at any time of the year
- Mostly the higher age groups are involved
- Confirmation by changes in CSF findings

(v) **Hypertensive Encephalopathy :**

- Onset is sudden
- Isolated single cases occur at any time of the year.

- Past history of hypertension.
- Uncontrolled hypertension prior to episode.
- Cerebral symptoms vary from person to person.

(vi) **Uraemic & Hepatic Coma :**

- The history of chronic illness, with signs and symptoms of underlying disease.
- Gradual onset and progressive deterioration of health.
- The signs and symptoms of renal or hepatic failure are present over a long period.
- Laboratory tests confirm the diagnosis.

(vii) **Diabetic Coma :**

- Gradual or sudden onset.
- Temperature is usually normal.
- Cases are usually isolated from a single locality.
- History of diabetes.
- The condition deteriorates fast.
- Confirm by urine and blood sugar examinations.

(viii) **Epilepsy :**

- Usually seen in children.
- Careful History will reveal similar attacks in the past.

(ix) **Other Clinical Entities :**

Other diseases to be excluded are :—

- Typhoid encephalopathy.

- Gram-negative septicaemia.
- Brain abscess
- Narcotic poisoning.

CHANGES IN CEREBROSPINAL FLUID IN CEREBRAL MALARIA AND OTHE DISEASES CONSIDERED FOR DIFFERENTIAL DIAGNOSIS

	NORMAL VALUES	MALARIA	MENINGITIS MENINGICOCCAL	TUBERCULAR	OTHER COCCAL	JAPANESE B. ENCEPHALITIS	SUB ARACHAOID HAEMORRHAGE	HYPERTENSIVE ENCEPHALOPATHY	HEPATIC ENCEPHAPOPATHY
Pressure	50 to 180 mmh 20	Normal to++	± to +	± to +	± to +	± to +	+ to ++	Normal to +	Normal
Character	clear and colourless	Normal	Normal or xanthochronic	clear	Normal or xanthochronic	Normal	Bloody or xanthochronic	Normal	Normal or xanthochronic
Cells	1-5/mm³								
-Polys	-	-	+++	-	+++	-	+to+++	Normal	-
-lymphos	1-5/mm³	+	-	+++	-	++	+to+++	Normal	+ to ++
Protein	15-40 mg/L								
-Globulin		+ to ++	+++	++	+++	± to +	± to +	± to +	± to +
-Albumin		++to+++	+++	++	+++	+ to ++	± to +	+ to ++	+ to ++
Sugar	40-70 mg/L	Normal or +	-to ±	± to +	-to ±	Normal	Normal	Normal	Normal
Chlorides	720 to 750 mg/L 116 to 122meq/L	Normal	±	- to ±	±	Normal	Normal	Normal	Normal
Micro organiss	Nil	Nil	± to +	±	± to +	Nil	Nil	Nil	Nil

2. ACUTE RENAL FAILURE

According to some studies acute renal failure occurs in approximately 10% of cerebra malaria cases. It is a reversible process but in some patients mainly adults, it leads to acut tubular necrosis thus leading to overall high Mortality.

The exact precipitating factors of acute renal failure in P. falciparum infection are no known. The renal anoxia due to impaired internal blood flow may be the main cause. The rena failure is indicated when 24 hour urinary output drops to 400 cc or below and serum creatinin is more than 3.0 mg/dl fails to improve even after rehydration.

In such condition, blood urea, serum creatinine and plasma potassium are raised, specific gravity of urine is about 1.00 or less. On the other hand, in cases of heat stroke, concentrated urine with normal microscopic appearance is due to dehydration.

In chronic cases of *P. malariae* kidney damage develops slowly over a period of time. The underlying pathological changes associated with nephrotic syndrome are focal hyalinising lesion and segmental endothelial cell proliferation. The thickening of capillary wall of basal membrane is due to deposition of antigen-antibody complex at the site.

3. PULMONARY OEDEMA

Occurs in *P. falciparum* malaria late in course but develops rapidly due to massive transudation of fluid in the lung alveoli.

- A variety of associated causes which trigger this condition are:
- (i) over hydration
- (ii) pregnancy
- (iii) cerebral malaria
- (iv) high parasitaemia (Density) of asexual forms of *pf* exceed 5% of erythrocytes in peripheral blood
- (v) hypotension
- (vi) acidosis
- (vii) uraemia.

If not treated promptly, it produces high mortality due to resultant hypoxia, dyspnoea and strain on cardio-vascular system.

The signs and symptoms are:—

- pulmonary distress such as shortness of breath, cyanosis, shallow rapid breathing increase in respiratory rate.
- rapid pulse.
- some times blood tinged sputum.
- basal crepitations.

4. GASTRO-INTESTINAL INVOLVEMENT

The symptoms are due to massive involvement of intestinal vascular bed leading to necrosis of intestinal mucosa and resultant congestion.

The important cardinal symptoms are :—

- Low blood pressure, high pulse rate
- Hyperpyrexia but later, in terminal cases hypothermia
- Anorexia, nausea, vomiting and abdominal pain
- Non-infective diarrhoea with blood stained stools
- Pronounced dehydration
- The symptoms may mimic any abdominal condition such as pancreatitis, biliary colic, typhoid, acute appendicitis.

The diagnosis is confirmed by blood examination for M.P.

5. ALGID MALARIA

The patient comes with typical signs and symptoms of shock and in a collapsed condition. The clinical picture shows :

- Cold, clammy skin, extremities are also cold
- High Rectal temperature, although oral temperature is low
- Lips and nails are cynosed, shallow laboured breathing, thin, pulse but fast and low B.P.
- P.C.V. high
- Blood slide positive for *P. falciparum*

The patient should be treated for shock and Anti malarials started.

6. HAEMOGLOBINURIA AND BLACK WATER FEVER

The name of this entity arises from the fact that in *P. falciparum* infection some cases pass black or smoky urine. It is believed that the condition is precipitated usually in non-immune cases treated with non-therapeutic doses of Quinine, which are usually taken irregularly. It may be related to Glucose-6-phosphate dehydrogenase deficiency status. Sometimes it may be a part of auto-immune reaction. There is massive haemolysis of red blood cells. This syndrome is not seen in infection with other species of plasmodium. It produces very high mortality, if not managed properly.

The cardinal clinical features are:

- High degree of anaemia, RBC count is as low as 1 mill/cmm.
- Low Hb levels.
- Urine—dark brown due to methaemoglobin or red when oxyhaemoglobin is present. It also contains Bile, albumin, hyaline and granular deposits, sometimes RBC casts may be present.
- Moderate to high parasite count in peripheral blood smear.

For differential diagnosis all other conditions producing haemoglobinuria should be considered.

7. LIVER DAMAGE—HAEMOLYTIC JAUNDICE

The liver damage is very rare in *P. falciparum* infection, it occurs due to excessive haemolysis, sudden load is sometimes so high that liver is not able to cope with it.

On clinical examination:—

- liver is enlarged, soft and tender.
- moderate to severe jaundice of haemolytic nature.

The condition usually clears up when antimalarials are given and parasitaemia as well as haemolysis are controlled. As the condition is usually associated with other severe manifestations of *P. falciparum* infection, its management forms a part of other complications.

8. ANAEMIA

Usually severe anaemia in *P. falciparum* infection is due to rapid and pronounced haemolysis, and is of normocytic, normochromic type. The RBC's destruction is due to two reasons, (i) destruction of parasitised RBCs which in untreated severe cases may be massive, (ii) the normal RBCs are destroyed due to toxins liberated by the parasite.

Thus the quantum of haemolysis is never directly proportional to parasite density levels in the blood. Sudden reduction in haemoglobin, similar to profuse loss of blood, is responsible for shock.

The entity rarely causes mortality, if proper treatment and management are carried out. However, in more prolonged infections, the anaemia is megaloblastic, hypochromic type. Severe anaemia when haematocrit less than 20% or haemoglobin less than 7.0 gm per dl.

9. HYPOGLYCAEMIA (BLOOD GLUCOSE LESS THAN 40 - mg/dl)

- It is a common complication in severe *P. falciparum* infection.
- It is a serious complication in pregnancy, children and during Post Partem period.
- Quinine in therapeutic doses can cause hypoglycaemia on account of excessive insulin release.
- It is to be treated as a medical emergency with I.V. 50% glucose while treatment is given with Quinine. Convulsions are usually not uncommon.

Milder symptoms are

- anxiety, breathlessness, confusion, oliguria, sweating, tachycardia, feeling of cold and headache.

10. DEHYDRATION

It is the most common complication in severe malaria infection with *P. falciparum* and other malaria parasite species. On account of hyperthermia and hyperventilation this complication is more often encountered in vulnerable age groups i.e. infants or young children.

The patient presents with :—

- Parched lips. The lips are dry and cracked.
- Pinched appearances due to excessive loss of water, face of the patient especially infants and young children gives sunken appearance.
- Skin is hot, sometimes wrinkled with loss of elasticity.
- The patient presents with unquenchable thirst.
- Oliguria or anuria is quite often present.
- The condition is serious in younger age group and requires immediate attention and proper management.

SECTION-II

P. FALCIPARUM INFECTION IN INFANTS AND CHILDREN

- ALL severe complications described above are more acute in case of infants and children due to their low immunity status.

- In early months of life, manifestations are mild with low grade parasitaemia (10%) because of passive immunity.

- Parasitaemia increases with age.

- In hyper endemic areas mortality rate is highest during first two years of life.

- Fever is continuous and very high and is quite often associated with cerebral symptoms of confusion and convulsions especially at the age of 6 months to 5 years.

- The associated gastro-intestinal symptoms are about persistent vomiting and diarrhoea.

- Renal failure is unusual.

In highly malaria endemic areas *P. falciparum* infection of local children during first five years of life can cause fatal illness.

The parasitological and other laboratory findings are same as described earlier. The management of case is more difficult but prompt antimalarial treatment with administration of oral or parentral therapy along with supportive treatment, the chances of recovery are good.

Table - 3.1 : Difference between severe *P. falciparum* malaria in adults and children

Signs and symptoms	Adults	Children
- Cough	Uncommon early symptom	Common early symptom
- Convulsions	Indicate cerebral involvement or hypoglycaemia	May indicate cerebral involvement or hypoglycaemia, but it could be a nonspecific consequence of fever.
- Duration of symptoms before features of severity develop.	Commonly Several days	Usually 1 - 2 days only
- Jaundice	Common	uncommon
- Time from start of treatment to resolution of coma in cerebral malaria.	Usually 2 - 4 days	Usually 1 - 2 days
- Hypoglycaemia	Uncommon, Usually Quinine - induced (especially in pregnancy) with hyperinsulinaemia. Sometimes pretreatment with low plasma insulin.	Common usually pretreatment, with proportionate decreased circulating insulin.
- Pulmonary oedema	Common	Rare
- Susceptibility toxicity of antimalarials	See above Quinine induced hypoglycaemia in adults.	More labile than adult to suffer circulatory collapse after parentral chloroquine if given rapidly.
- Renal failure	Common	Rare
- Neurological sequelae.	Uncommon	occurs in about 10% of cases
- Cerebro spinal fluid (CSF)		
- pressure	Normal	Variable
- changes	Normal	Normal

SECTION-III

MALARIA IN PREGNANCY

- Although all other manifestations of malaria are more or less same in a pregnant woman, except that the placenta is heavily loaded with *P. falciparum*, blood stages and their concentration is higher than in any other organ due to preferential parasitic sequestration. This pathology results in decreased blood flow to placenta leading to foetal anoxaemia. Foetal distress may cause intra - uterine death with miscarriage or abortion. In case, the above complication does not arise, then due to lowered oxygen tension and flow of nutrients from placenta to foetus the foetal development is retarded and low birth weight babies are common in malarious areas. Malaria in pregnant women is associated with high maternal and foetal mortality.

- Other common complications in pregnant women are renal failure, eclampsia, acute pulmonary Oedema, hypoglycemia and anaemia.

- In hyperendemic areas in a primigravida there is increased parasitaemia and serious effects of malaria when compared to multigravida.

> To arrive at correct and quick diagnosis, the pathological investigations should start with examination of peripheral blood for malaria parasite.

Some of the investigations to be carried out are :

(i) Blood pressure

(ii) Microscopic examination of peripheral blood smear for M. P. to be repeated after every 6 - 8 hours as long as the slide is negative, if positive parasite count may be done.

(Note : In rare cases the peripheral blood smear may be initially negative since all parasites are in late trophozoite/schizont stage and are sequestrated in capillaries of internal organs. They will come to peripheral circulation at a later stage as rings and can be recognised microscopically. This process may take 6 to 12 hours).

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(iii) Total RBC count

(iv) HB % estimation

(v) Total WBC and differential count

(vi) ESR

(vii) C.S.F. examination

(viii) P.C.V.

(ix) Blood chemistry (Blood urea, serum bilirubin, Blood sugar, Serum electrolytes and Serum creatinine)

(x) Urine examination — Routine
— Microscopic

(xi) Viral and bacteriological studies

Other biochemical or pathological tests, if required, may be carried out during the course of treatment to see the progress of the case.

BLOOD PICTURE IN MALARIA

STATUS OF RBC's :

Total RBC count is reduced, poikilocytosis, polychromasia and Anisocytosis.

INACUTE ATTACK :

Normochromic, Normocytic anaemia

INCHRONIC ATTACK :

Reticulocyte count increases, nucleated RBCs are rarely seen in severe anaemia.

HAEMOGLOBIN :

Hb falls rapidly—a fall of 0.5 to 1 mg. per day in high parasite densities during acut attack has been seen in a number of cases.

PACKED CELL VOLUME :

Low, sometimes as low as 20%.

PALTELETS :

Thrombocytopenia of varying degrees.

WBCs :

EARLY STAGES :

Leucocytosis of varying degree.

LONG STANDING CASES :

Leucopenia.

PLASMA PROTEINS :

Reduced.

ALBUMIN/GLOBULIN RATIO :

Altered.

ERYTHROCYTE SEDIMENTATION RATE :

Increased, more pronounced in acute cases and severe anaemia.

SERUM BILIRUBIN :

Raised.

BLOOD SUGAR :

Variable, sometimes raised during hyperpyrexia, low in acute severe cases with P. falciparum infections.

BLOOD UREA :

Raised in renal dysfunction.

SERUM CREATININE :

Increased in renal failure.

ELECTROLYTES :

Electrolyte imbalance with acidosis : - sodium/potassium ratio altered.

URINARY CHANGES IN MALARIA

In acute *P. falciparum* infection :

1. Urine output : low in case of acute renal failure (less than 400 cc per day).
2. Specific gravity : 1.00 or less.
3. Albumin : present in traces.
4. Urobilinogen : high.
5. Sodium/potassium ratio : altered.
6. RBCs : occasionally present in low numbers.
7. Casts : hyaline and granular present.
8. Haemoglobin—present largely as Oxyhaemoglobin and Methaemoglobin in complicated malaria cases such as Black Water Fever.

ANY ONE OF THE ABOVE ABNORMALITIES MAY BE PRESENT IN A MALARIA CASE, BUT URINARY CHANGES IN ACUTE *P. VIVAX* OR *P. MALARIAE* INFECTION ARE RARE.

ERRORS IN DIAGNOSIS

FAILURE TO EXAMINE BLOOD SMEAR : The commonest error in diagnosis of malaria is the failure to examine blood film in a fever case. The fever in malaria may not show typical stages of malaria paroxysm and it may not be very high. Sometimes the fever is accompanied with other signs and symptoms which may not be strong enough to suggest clinical diagnosis of malaria. However, it is imperative that all fever cases should be subjected to microscopic blood examination for malaria parasite to exclude any possibility of malaria infection.

FAILURE TO TAKE HISTORY OF MOVEMENT : In non-malarious areas, the physician may forget to take the history of movement of the patient and thus miss the clinical diagnosis of malaria. The incubation period in plasmodium infection is usually from 9 to 2 days therefor, unless history of movement is taken in a fever case it may not be possible to exclude malaria infection by any degree of certainty because prior to incubation period the patient might have visited endemic area during the transmission season. A treatin

physician should always elicit the history of movement of the patient during the fortnight preceding the first fever episode.

FAILURE TO REALISE SEVERITY OF THE DISEASE : This lapse may result in development of further complications and increase the chances of mortality in a patient. Sometimes even in a patient with low grade temperature, the parasitaemia levels may be high as is seen in algid malaria due to *P. falciparum* infection. In these cases, rectal temperature is usually high and will point towards severity of the disease. Therefore, in malarious areas, where *P. falciparum* infection is predominant, a physician should be careful to consider all signs and symptoms and during physical examination should record rectal temperature so as not to miss the severity of fever. He should very carefully conduct systemic examination of the patient. He should also note whether there is amelioration of symptoms after medication or the symptoms continue or their severity increases.

ERRORS IN MICROSCOPIC DIAGNOSIS

These errors arise due to inefficiency of laboratory technicians, faulty collection of blood smears and failure to examine requisite number of fields in thick smears of suspected malaria case. The errors may also arise due to poor staining of blood smears and artefacts therein.

FAULTY DIFFERENTIAL DIAGNOSIS

If a treating physician does not take all precautions and fails to consider all aspects of differential diagnosis of malaria, he is likely to miss a malaria case.

On account of the extensive malaria control operations undertaken all over the country, clinical presentation of malaria case is modified in different paradigms of malaria. In areas where malaria transmission is interrupted or at a low level, the non-immune population will present with clinical signs & symptoms with wide variation depending on the immune status of the patient, on account of the previous exposure to malaria or general innate immunity levels of the person which determines the response of individual to parasitic infection. These patients present mixed clinical picture, whereas in children symptoms are more pronounced. In hyper endemic areas, the clinical picture in adults is more or less uniform due to frequent exposure to malaria. But in infants and young children upto 5 years of age the signs and symptoms vary in intensity. Therefore, a practising physician should update his knowledge of malaria indemicity in the locality.

The Directorate of NAMP has laid down some general principles for clinical diagnosis of malaria case which are not very exhaustive but may be useful for a practising physician. However, no clear-cut guidelines can be laid down for proceeding with the differential diagnosis but a physician after considering various aspects of the presenting fever episode in a patient should carry out the laboratory examination to exclude

other diseases. The guidelines given by the NAMP are reproduced below :—

Suspected Malaria

All fever cases unless proved negative for malaria parasite on microscopy.

Probable Malaria: Clinically diagnosed

Fever cases without the following associated symptoms and not subjected to microscopic examination may be suspected and reported separately as clinical malaria cases :—

1. Cough—Acute respiratory infections.
2. Cold with running nose.
3. Skin rash suggestive of eruptive illness.
4. Burning micturition.
5. Skin infection e.g. boils, abscess, infected wounds.
6. Painful swelling of joints.
7. Ear discharge.
8. Fever in Infective Hepatitis.
9. In non-endemic areas spleenomegaly with irregular fever, skin pigmentation is suggestive of kala-azar.
10. Lymphangitis and lymph adenitis in filaria endemic areas.

Seriously sick

Seriously sick malaria cases are those who present with following signs and symptoms:—

- Cerebral malaria—Case of unarousable coma not attributable to any other cause in a patient with *P. falciparum* infection.

Other cases, with hyperpyrexia, convulsions, severe anaemia, pregnancy with fever, pulmonary oedema in *P. falciparum* infection, anaemia and malarial haemoglobinuria.

Deaths due to Malaria	-	Malaria deaths can only be due to *P. falciparum* infection.
	-	Deaths are very common in cerebral malaria cases and other serious complications in *P. falciparum* infection.
	-	If any patients with fever case having signs and symptoms cited above dies without microscopic confirmation, the death can be attributed to malaria.
Confirmed Malaria Death	-	Death of microscopically confirmed *P. falciparum* infected patient due to any of the complications mentioned above.

MISSED HYPOGLYCAEMIA

One of the serious complications of *P. falciparum* malaria is hypoglycaemia. Sometimes during acute stage and hyperpyrexia, the blood sugar levels may go high but usually *P. falciparum* malaria precipitates hypoglycaemia. It may present in a more severe form in diabetic patients, children and infants. Therefore, laboratory investigations for blood sugar levels are important in complicated malaria cases, so that immediate steps could be taken to correct hypoglycaemia.

SECTION-IV

TREATMENT AND MANAGEMENT OF MALARIA PATIENTS

The case management in malaria comprises of three aspects :—

1. Specific treatment with antimalarials.
2. Supportive symptomatic treatment.
3. Specialised nursing care in severe and complicated malaria cases.

If clinical signs and symptoms indicate strong evidence of malaria, the physician should proceed with microscopic confirmation of malaria parasite, blood picture, haemoglobin percentage and other tests. However, he should not wait for microscopic confirmation and start the treatment immediately.

Before going into the specific aspects of treatment and management of malaria cases, it is necessary to familiarise with different terminologies used in the treatment of malaria.

Blood schizonticidal drugs	-	Drugs which act on asexual forms of malaria parasite i.e. ring, trophozoite, schizont.
Tissues schizonticidal drugs	-	Drugs which act on asexual forms of malaria parasite in the liver i.e. the primary tissue schizont of pre-erythrocytic forms in liver.
	-	Hypnozoites or late tissue schizonts are affected by primaquine.
Gametocytocidal drugs	-	Drugs which act on sexual forms of malaria parasite.
Sporontocidal drugs	-	Drugs when given to infected persons prevent development of parasite in the mosquito.

Terminology used for Treatment Schedules of Malaria

Suppressive treatment	-	It prevents appearance of clinical symptoms of parasitaemia by early destruction of erythrocytic stages of parasite. It does not necessarily prevent or eliminate malaria infection. In patients

parasitaemia and clinical symptoms may sometimes develop when suppressive treatment is withdrawn.

Radical Treatment - It aims at achieving complete parasite cure and in case of *P. vivax* preventing relapses by destroying hypnozoites which is achieved by administration of proper antimalarials like primaquine, which has effect on hypnozoites. The radical treatment acts on gametocytes also. This prevents further transmission of malaria from an infected person.

Presumptive Treatment - Presumptive treatment is administered to all suspected cases of malaria i.e. all fever cases in the locality. Such a treatment consists of a single/multiple doses of schizonticidal drug like chloroquine. The objective is to achieve remission of symptoms till the diagnosis is confirmed microscopically and radical treatment can be administered.

Mass Drug Administration - Usually it is a part of malaria control operations where all fever cases or general population of a particular group of persons of the locality such as children, pregnant women and migratory labourers are given combination of schizonticidal and gametocytocidal drugs to achieve remission of parasitaemia and liquidation of gametocytes.

Clinical cure - For clinical cure, schizonticidal drugs are administered to achieve remission of clinical symptoms and parasitaemia.

Chemoprophylaxis - It is aimed at prevention of disease manifestations in the individuals. It does not prevent infection with malaria parasite because no sporozoites, (absolute prophylaxis) but

causal prophylactic drug given in repeated doses a
weekly interval prevents appearance of clinical sign
and symptoms and parasitaemia in the person.

MANAGEMENT OF UNCOMPLICATED MALARIA

Physician's Options

Out of a large number of antimalarial compounds available for treatment of malaria, the physician while treating a malaria case has to decide the drug of choice. The options available are :

(i) The route of administration—oral, intramuscular, or intravenous,

(ii) Rapidity of absorption from the route of administration,

(iii) Time taken to achieve therapeutically effective blood concentration,

(iv) Half life of the drug,

(v) Excretion time/rate,

(vi) Adverse reactions such as idiosyncracy, chronic toxicity on prolonged use,

(vii) Contraindications,

(viii) Precautions to be observed as well as the efficacy of antidotes available for treatment of acute or chronic toxicity and

(ix) Nursing care required if adverse reactions are encountered.

General Rules of Antimalarial Therapy

Before the details regarding the mode of action, dosage etc. of different antimalarials are discussed, it is necessary to lay down some ground rules for use of antimalarials. These rules will help the physician in choosing appropriate treatment schedule for a patient suffering from malaria.

1. Oral administration of antimalarials should be preferred in all cases who can swallow and retain antimalarial compounds, as most antimalarials are absorbed rapidly.

2. Intravenous antimalarials like Quinine or Artemisinin should be used in comatosed patients or patients who cannot retain drugs administered orally, because of gastrointestinal irritation.

3. An antimalarial with good chemotherapeutic index (difference between clinically effective and toxic dosage) should be chosen for oral and parentral administration.

4. Chloroquine is the drug of choice for treatment of *P. vivax*, *P. malaria* and *P. falciparum*.

5. Only in cases where infection with *P. falciparum* strain resistant to Chloroquinine is suspected, other antimalarials should be used.

   (a) In ambulatory cases of *P. falciparum* resistant strain without complications, long acting Sulpha-Pyrimethamine combination is the drug of choice.

   (b) In severe and complicated malaria, intravenous Quinine should be administered.

6. Internationally accepted dosage should be strictly adhered to, so that future complications and toxic manifestations are avoided.

7. While administering the intravenous Quinine, patients should be carefully monitored for hypoglycaemic crisis and cardiovascular complications and suitable supportive treatment.

In uncomplicated malaria, the treatment is directed towards achieving clinical and parasitological cure by administration of oral Chloroquine phosphate in a single dose of 10 mg. per kg body weight. In cases microscopically confirmed to be suffering from *P. falciparum* infection, in areas where *P. falciparum* resistance or refractory strains to Chloroquine are present, in the first instance, oral Chloroquine is still the drug of choice and is given in three divided doses, i.e. on first and second day @ 10 mg. per kg body weight and on the third day a dose of 5 mg. per kg/body weight is administered. Usually the treatment with Chloroquine is adequate for achieving parasitological cure almost all over the country. But in areas where *P. falciparum* resistant strains are present and a *P. falciparum* case fails to respond to Chloroquine, a single dose of 1.5 gm of long acting Sulpha combination with 75 mg Pyrimethamine is administered.

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MANAGEMENT OF ASSOCIATED SIGNS AND SYMPTOMS

Hyperthermia

To control hyperthermia, hydrotherapy is recommended with tepid water sponging of the face and limbs. If the temperature is above 103° F, the sponging is to be continued till temperature is brought down to 101° F. In cases of severe hyperthermia the patient can be covered with bedsheets soaked in water and put under a fan, till the temperature is brought down to 101° F. It is usually beneficial if the patient is kept in an air-conditioned or air cooled room with adequate humidity which prevents rapid loss of fluid from body. Paracetamol is the drug of choice given at the rate of 5 mg./kg. body weight orally or if needed parentrally in suitable divided doses.

Dehydration

To combat dehydration, intravenous fluid, saline or glucose is required. The intravenous infusion of glucose is more appropriate for *P. falciparum* infection on account of the danger of hypoglycaemia in this infection. It is necessary to maintain slightly negative fluid balance because of a danger of pulmonary congestion which is quite frequently observed in malaria infection especially in case of *P. falciparum.*

Management of Convulsions

In a case of uncomplicated malaria, due to hyperthermia, infants and young children may develop convulsions which are managed by intramuscular or intravenous Diazepam in the dose of 0.15 mg per kg/body weight. Diazepam can be administered at 8 hourly interval till convulsions are controlled.

Management of disorientation

In young children, the hyperpyrexia sometimes results in disorientation. It can be managed by bringing down the Fever. Administration of tranquilisers is usually not necessary. A close watch should be kept on fluid intake and output.

A complete parasitological cure is achieved after administration of radical treatment to the patient which should include Primaquinine in appropriate dosage. The dose of Primaquinine and other antimalarials have been given separately.

Correction of Anaemia

As most cases of malaria are anaemic to begin with or develop anaemia during the course of infection on account of rapid destruction of RBCs and loss of haemoglobin, the treatment for anaemia should be simultaneously instituted with oral iron and folic acid in appropriate dosage. However, if haemoglobin is less than 7 gm/dl, it is beneficial to give blood transfusion.

C. SPECIFIC TREATMENT

Commonly marketed and extensively used antimalarials in India have been mentioned in the previous section.

There are other antimalarials which were used earlier but are no longer utilized. These drugs are : (1) Mepacrine, Atebrine (2) Proguanil, Chlorproguanil, Cycloguanil (3) Pamaquinine, Quinocide, Plasmochin (4) Dapsone (5) Sulfonamides. These drugs are more toxic and their action is comparatively poorer as compared to drugs now recommended.

New Antimalarial Drugs

New antimalarials which are found to be very effective in the treatment of malaria but are not currently marketed in India are :— (1) Mefloquine (2) Qinghausu derivatives (3) Mefloquine combination with long acting Sulpha (4) Halofantrine.

Some General Remarks About Antimalarials

QUININE IN DOSAGES PRESCRIBED FOR TREATMENT OF MALARIA DOES NOT INDUCE ABORTION OR MISCARRIAGE IN PREGNANT WOMEN. RISK OF ABORTION IS HIGHER IN UNTREATED CASES.

CHLOROQUINE RESISTANT CASES WHO ARE ALLERGIC TO SULPHA DRUGS ARE TO BE TREATED WITH QUININE OR A COMBINATION OF QUININE AND TETRACYCLINE.

LONG ACTING SULPHA AND PYRIMETHAMINE COMBINATION HAS VERY LITTLE EFFECT ON P.VIVAX AND WILL NOT GIVE CLINICAL RELIEF IN SUCH CASES BUT IT IS THE DRUG OF CHOICE FOR ORAL ADMINISTRATION IN INFECTION WITH CHLOROQUINE RESISTANT STRAIN OF *P. FALCIPARUM*. ITS ACTION IS SLOW.

PROLONGED USE OF LONG ACTING SULPHA COMBINATION CAN PRODUCE STEVENSJOHNSON SYNDROME, AGRANULOCYTOSIS, AND APLASTIC ANAEMIA.

THESE DRUGS ARE NOT SUITABLE FOR PROLONGED SUPPRESSIVE TREATMENT.

THEIR DOSAGE SCHEDULE SHOULD BE FOLLOWED STRICTLY.

THEY SHOULD BE GIVEN TO INFANTS AND PREGNANT WOMEN WITH CAUTION.

THERE IS HIGHER RISK OF DEATH ON ACCOUNT OF PROLONGED USE OF SULPHA COMBINATION AS SUPPRESSIVE/PROPHYLACTIC THAN THAT WITH P. FALCIPARUM INFECTION PROVIDED THE CASE IS DETECTED AND TREATED IN TIME.

CHLOROQUINE, PRIMAQUINE OR PYRIMETHAMINE SHOULD NEVER BE GIVEN ON EMPTY STOMACH.

PATIENTS HAVING GASTRO-INTESTINAL UPSET OR THOSE WHO CANNOT TAKE OR RETAIN ORAL DRUGS SHOULD BE GIVEN PARENTRAL ANTIMALARIALS EVEN IF THEY ARE CONSCIOUS.

DURING ADMINISTRATION OF PRIMAQUINE, LOOK FOR ACUTE TOXICITY CYANOSIS AND SMOKY URINE.

IF PRESENT :

STOP THE DRUG:

OBSERVE THE CASE.

TRANSFER SERIOUS CASES TO HOSPITAL.

AFTER ADMINISTRATION OF PRIMAQUINE, GAMETOCYTES MAY BE SEEN FOR A FEW DAYS IN PERIPHERAL CIRCULATION BUT THEY ARE NO LONGER INFECTIVE TO MOSQUITOES AS THEY BECOME NON-FERTILE.

PRIMAQUINE SHOULD NEVER BE GIVEN TO PREGNANT WOMEN OR INFANTS

I. *P. falciparum* infection

There is a direct relationship between case fatality and time lag between onset of attack and starting of specific treatment, especially in cerebral malaria.

BASED ON RESULTS OF SEVERAL STUDIES, IT IS ESTIMATED THAT ONLY 0.5 TO 2% OF *P. FALCIPARUM* CASES DEVELOP SERIOUS COMPLICATIONS.

IN PROPERLY MANAGED AND TREATED PATIENTS, FATALITY RATE OF CASES WITH SERIOUS COMPLICATIONS ARE LESS THAN 20%.

TO REDUCE PERIOD OF MORBIDITY AND TO PREVENT MORTALITY IN CLINICALLY DIAGNOSED CASES, ADMINISTRATION OF SPECIFIC AND MOST SUITABLE ANTIMALARIAL SHOULD BE STARTED IMMEDIATELY WITHOUT WAITING FOR LABORATORY REPORT WHICH WILL FOLLOW IN DUE COURSE.

Treatment of a microscopically confirmed case of *P. falciparum* infection :

Patient who can ingest and retain oral drug :

(a) In areas with Chloroquine sensitive strain :

Chloroquine (base) 1500 mg — 600 mg first day
600 mg second day
300 mg third day

plus

If other complications are not there and haemoglobin is above 7—8 gms. a single dose of Primaquine 45 mg (0.75 mg per kg/b.w.) is given on first day for its gametocytocidal action.

(b) Areas with > 25% RI and RII incidence of chloroquine resistant strain, the drug of choice and its schedule is :—

Long acting Sulpha	—	1.5 gm	i.e. 3 tablets as a single dose
+Pyrimethamine	—	75 mg	+45 mg. Primaquine

(Usually Primaquine is given on the next day and not along with long acting sulpha)

Note : The information on Chloroquine resistant areas keeps on changing. The latest information can be obtained from the office of the Regional Director, Regional office for Health & Family Welfare and Directorate of National Anti Malaria Programme.

IN SEMICONSCIOUS OR COMATOSED PATIENTS OF SEVERE *P. FALCIPARUM* INFECTION

QUININE SHOULD BE GIVEN WELL-DILUTED AND SLOWLY BY I.V. INFUSION. IT IS THE DRUG OF CHOICE IN PREGNANT WOMEN AND INFANTS

(a). Inj. Quinine I/V 10 mg/kg body wt. (600 mg), 8 hourly, (total 24 hour intake should not exceed 2 gms in an adult) till the patient regains consciousness and is able to take drug orally. Oral Quinine 600 mg TDS is to be continued for seven to ten days. When adequate facilities for management of complications arising out of Quinine toxicity are available, a loading dose of Quinine dihydrochloride 20 mg per kg body weight as infusion is given, and it should be well diluted with 500 ml of 5 per cent glucose. Infusion is given over a period of 5 hours (2 ml per minute). If I.V. facility is not available, deep intramuscular dose of 10 mg per kg body wt. is given 8 hourly. I.M. injections produce complications which, sometimes in the long run, are crippling if proper precautions are not taken.

(b) **Chloroquine**

CHLOROQUINE IS NOT WELL TOLERATED SPECIALLY BY INFANTS OR YOUNG CHILDREN. I.M./I. V. INJECTION SHOULD NOT BE GIVEN TO THEM.

IN A PATIENT OF ANY AGE IT MAY PRODUCE LOW BLOOD PRESSURE, SUDDEN COLLAPSE, WITH HIGH MORTALITY.

PARENTRAL ADMINISTRATION OF CHLOROQUINE IS MORE HAZARDOUS THAN PARENTRAL ADMINISTRATION OF QUININE AND IS NOT RECOMMENDED BECAUSE OF ADVERSE REACTIONS CAUSING FALL IN BLOOD PRESSURE AND CARDIAC ARRYTHMIAS.

IN SEVERE MALARIA CASES I.M. INJECTION OF ANTI MALARIAL SHOULD NOT BE GIVEN DUE TO FAULTY PERIPHERAL CIRCULATION AND ERRATIC ABSORPTION OF DRUG.

However, if quinine is not available and only Chloroquine I.V. preparation is available, it is given in doses of 3.5 mg/kg b.w. 8 hourly slowly in isotonic fluid. Total 24 hour dose should not exceed 600 mg base (up to 10 mg/kg body weight). Dose of Inj. Chloroquine I.M. is 5 mg per kg/b.w.

MANAGEMENT OF OTHER SIGNS AND SYMPTOMS

(i)	Hyperpyrexia (Rectal Temperature above 39°C)	(i)	Tepid sponging.
		(ii)	If the temperature is 39°C or above, remove patient's clothes and cover him with towel or sheet soaked in tepid water and keep him under the fan.
		(iii)	Keep patient in an air-conditioned room, if possible.
		(iv)	Paracetamol : 5 mg kg/b.w. parental administration, if required.
(ii)	Dehydration	(i)	I/V Glucose saline measure urine output, maintain slightly negative fluid balance to avoid pulmonary complications.
(iii)	Acute renal failure with Anurea or oligurea and Black Water. Fever	It must be managed with proper biochemical examination of blood, serum sectrolytes and E.C.G., etc.	
		(i)	I/V glucose saline to correct dehydration—If this fails to induce urine secretion and output remains less than 60 cc per hour give:—
		(ii)	Frusemide 20 mg or as required, up to 500 mg, I.V. or I.M. as considered appropriate.
		(iii)	Keep watch on urinary output constantly.
		(iv)	If no improvement, put the patient on Haemodialysis or Peritonial dialysis without any further delay.
		(v)	Keep watch on serum creatinine, blood urea and serum potassium levels.
		(vi)	Alkalinise the urine if haemoglobinuria.

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		(vii)	Maintain diet control and restrict protein intake to 20 to 30 gm per day.
(iv)	Hyperkaliemia		Serum potassium should be kept below 5 mg/Lit.
		(i)	20 units Inj Insulin with glucose, 50 gm repeat as required.
		(ii)	Oral administration of exchange resin such as calcium bicarb.
		(iii)	I.V. calcium gluconate 10 to 20 cc. Repeat as required.
(v)	Hypokaliemia		Occurs with excessive diuresis after recovery in renal failure.
		(i)	10 cc potassium chloride in 24 hours or equivalent.
(vi)	Pulmonary Oedema		Arterial blood gases are monitored if the patient shows evidence of cyanosis, pneumonia or hyperventilation.
		(i)	Prop up at 45°
		(ii)	Oxygen
		(iii)	Keep careful watch on fluid balance
		(iv)	Monitor central venous pressure
		(v)	Venesect 250 ml blood into donor bag to be used later on
		(vi)	Give diuretic
(vii)	Gastro Intestinal complications	(i)	I.V. fluids.
		(ii)	Inj : Chlorpromazine to control vomiting.
(viii)	Bleeding	(i)	Parenteral Vit K, dosage to be regulated as per patient's condition.
		(ii)	Fresh whole blood transfusion.
(ix)	Jaundice & Liver damage	(i)	I.V. Glucose
		(ii)	Restrict fats
		(iii)	Vit K and B complex supplements
		(iv)	Bed rest

(x)	Shock	(i)	I.V. Plasma expanders
		(ii)	Corticosteroids if condition indicates use upto 100 mg 8 hourly.
		(iii)	Dopamine drip
		-	if associated with high parasitaemia
(xi)	Anaemia (P.C.V. 20% Hb less than 7 gm)		
		(i)	Whole fresh blood transfusion
		(ii)	Pack cell transfusion
		(iii)	Once condition improves add Iron and Folic acid supplements.
(xii)	Convulsions	-	Mostly due to hyperpyrexia
		-	Specially in children in both *p. vivax* and *p. falciparum* infections
		(i)	Inj Diazepam 0.2 mg per kg/b.w. IM or IV 8 hourly dose to be regulated by patient's response *or* Inj Phention sodium 5 mg per kg/b.w. slow I/V infusion over 15-20 minutes.
		(ii)	Inj Phenobarb 5 to 10 mg per kg b.w. as prophylactic
(xiii)	Hypoglycaemia	-	I.V. glucose 50% (up to 1 ml. per kg body weight) followed by I/V glucose 5 to 10%. Keep constant watch on blood sugar levels.
(xiv)	Hyperparasitaemia (parasitised RBCs 10% or above)	-	Exchange transfusion

Nursing care

Nurse the patient on the side as vomiting is common. Turn regularly at 2 hours interval or make the patient lie down on semi prone position.

1. Keep air passages clean
2. Give Oxygen if signs of air hunger
3. Prop up patient at 45° if hypostatic lung congestion.
4. Record temperature (rectal), pulse and blood pressure 2 hourly.
5. Tepid sponging when required.
6. Note fluid intake both oral and I.V.

	7.	Record urinary output. Put indwelling catheter if needed.
	8.	Note number and size of stools.
Laboratory follow-up	1.	Examine blood slide for M.P. at 6 to 8 hourly intervals till parasite clearance.
	2.	Repeat tests to watch P.C.V., anaemia, acidosis, jaundice, hepatic and renal failure and blood sugar for hypoglycaemia.

ERRORS IN MANAGEMENT OF SEVERE FALCIPARUM MALARIA

1. Misdiagnosis
2. Wrong assessment of severity
3. Faulty parasitology
4. Missed associated diseases/complications
5. Missed hypoglycaemia
6. Errors of antimalarial therapy
7. Deficient nursing
8. Errors of antimalarial therapy

(a) Delay (b) Wrong and exaggerated fear of drug toxicity such as Ingestion of Quinine (c) Wrong dosage (d) Wrong route of drug therapy (e) Early cessation of treatment (f) Delay in the treatment of pregnant women with malaria.

9. Mismanagement of respiratory complications
10. Failure to control convulsions
11. Lack of treatment for severe anaemia
12. Inappropriate adjuvant therapies
13. Delay in starting dialysis
14. Delay in giving blood transfusion.

TREATMENT OF INFANTS & CHILDREN

Drug Treatment

(a) Uncomplicated acute attack with *P.vivaxi/P. falciparum*:--Chloroquine is the drug of choice. Total dose 25 mg per kg body weight administered over three days—10 mg on first and second day, 5 mg on third day. Do not use parentral route, as far as possible because it is not well tolerated by younger age group and adverse reactions are encountered.

(b) Suspected infection with resistant strain of *P. falciparum*:— Where temperature does not come down/parasites do not disappear in 72 hours—such cases are given I/V Quinine or Sulpha (sulfadoxine or sulphalene) plus pyrimethamine combination orally.

- Sulpha combinations act very slowly, therefore evaluate clinical condition frequently.

MANAGEMENT IN PREGNANCY

A good prognosis can be expected, if case is treated as medical emergency. It requires:—

- Early diagnosis.

- Administration of antimalarials in adequate dosages. In severe cases, Quinine should be given intravenously. The dosage regimen advocated does not precipitate abortion. Risk of abortion is higher in untreated cases.

- All other supportive treatment should be given depending on clinical picture.

- During pregnancy the chemoprophylaxis in high risk malarious areas with small weekly single doses of chloroquine or chloroquine with proguanil in areas with *P. falciparum* chloroquine resistant foci may help in improving the health of child and mother, but is not advocated in areas with low or moderate risk of malaria.

- Iron deficiency anaemia should be promptly controlled and high levels of haemoglobin should be maintained throughout the pregnancy. If condition of the patient warrants, blood or pack cell transfusion should be given.

"DO'S"

Initial management of patients with severe malaria:

1. Must use referral services early.
2. Keep patient in a semi-prone position with proper nursing care.
3. Make a rapid clinical assessment and take blood for diagnostic purpose.
4. Calculate dose of drug.
5. Commence with antimalarial treatment early.
6. Check blood sugar to exclude hypoglycaemia, gluco strip method can be used for rapid assessment, follow-up with regular blood sugar estimation. If facility is not available, give I.V. glucose and check urine for sugar at regular intervals.
7. Assess state of hydration and measure urine output.
8. For younger age group, use anticonvulsant drug. (phenobarbitone 5-10 mg per kg/b. w.).
9. If temperature (rectal) is 39° C or above, tepid sponging, antipyretics and put the patient in a cool place.
10. Lumbar puncture to exclude meningitis.
11. Patient should be constantly watched for prevention or early detection and treatment of complications.

"DON'TS"

The following are not to be used as supportive treatment:—

1. Corticosteroids - Dexamethasone (prolongs coma)
2. Mannitol urea.
3. Heparin
4. Adrenaline

II. *P. vivax* infection

The radical treatment in *P. vivax* is for anti-relapse action. Primaquine is the drug of choice. However, Chloroquine is given along with it so that clearance of asexual stages is also achieved.

Dosage schedule

Chloroquine 10 mg/kg body weight+primaquine 0.25 mg/kg body weight (Adult dose 600 mg Chloroquine and 15 mg Primaquine on day one and 15 Primaquine alone daily for next four days).

Note : (i) Drug should be kept out of reach of young children. A single dose of 1.5 to 2 gm may be fatal to a toddler.

(ii) *If a* P. malariae *case is encountered, it should be treated as P. vivax case.*

(iii) *Do not administer the drug on empty stomach.*

(iv) *Discontinue Primaquine if toxic effects are observed.*

In Indian programme for radical treatment of *P. vivax,* primaquine is given for five days (15 mg per day in an adult). The 14 day radical treatment schedule advocated by some authorities for *P. vivax* is not considered necessary because difference between relapse rate with these two regiments is not very significant. In a control programme, five day schedule is acceptable and operationally feasible under Primary Health Care System. However, if a refractory case is seen, the patient may be given primaquine for 14 days under direct medical supervision, because of likely complications and emergency arising due to G-6-PD deficiency.

SECTION - I

MODULAR EXERCISES/CASE STUDIES ON THE DIAGNOSIS AND MANAGEMENT OF SEVERE AND COMPLICATED MALARIA

LEARNING OBJECTIVES

By the end of this unit you should be able :—

- To assess the severity of the disease in adults.
- To assess the severity of the disease in children.
- To determine what malaria specific treatment to be provided by which route and in what doses.
- To decide which investigation needs to be carried out and when.
- To provide appropriate management of the patient for various complications of severe malaria.

CASE STUDY : PATIENT 1

A woman from Punjab, aged 25 years, wife of an officer in Assam Rifles is brought to a central hospital at Dimapur (Nagaland). She is in the seventh month of her first pregnancy.

The patient became ill five days ago, with chills, sweating and headaches. An antibiotic was prescribed and her condition seemed to improve, but yesterday she developed rigors and persistant vomiting. A blood film at the local clinic revealed malaria parasites, and oral quinine (600 mg every 8 hours) was prescribed. She took two doses.

Today she has been referred to a central hospital because of restlessness and increasing mental confusion. Examination reveals a semiconscious woman, who is unable to converse. She responds to painful stimuli.

There is no neck stiffness, jaundice, palor or rash Axillary temperature is 39°C, pulse 90 beats/min., blood pressure 110/70 mm Hg. The uterine fundus is palpable (26-28 weeks), and the foetal heart can be heard.

Question 1

What tests are urgently required ?

Question 2

If the blood glucose is 1.2 mmol/1, what treatment will you prescribe ?

Question 3

If the blood film shows *P. falciparum* rings '++++', and the cerebrospinal fluid is normal except for low glucose, then :

(a) what antimalarial drug will you administer and by which route ?

(b) would you prefer an alternative to quinine because the patient is pregnant ?

(c) would you give a loading dose of quinine ? (Justify your answer).

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(d) what nursing procedures are important during this treatmènt ?

Question 4

After six hours the patient becomes increasingly restless. The respiratory rate increases to 40/minute. The blood glucose level is normal. Under these conditions, what special observations would you make ?

Question 5

What other observations are particularly important in this patient ?

Question 6

What other questions would you ask the patient's relatives ?

CASE STUDY : PATIENT 2

In PHC Baroda, District Kalahandi, Orissa various antimalarial drugs are available, but intravenous infusions cannot be given.

A child aged 20 months became feverish two days ago and has vomitted several times a today. One hour ago the child had convulsions described by the mother as a repetitive twitching of limbs and mouth, followed by unresponsiveness for few minutes. The child is now febrile (30°C), conscious, and able to localise and respond to a painful stimulus. A thick blood film shows *P. falciparum* rings '++++'. The child repeatedly vomits any antimalarial drug given by mouth.

Question 1

(a) Does the child have cerebral malaria ?

(b) What should you do about the convulsion ?

Question 2

The district hospital is 30 Km away; journey will probably take several hours by bus

(a) Should the patient be referred to hospital ?

(b) What treatment will you give meanwhile ?

Question 3

The child successfully took the second and third doses of quinine by mouth and was brought back to the clinic next day; there had been little change; the child was still febrile, and the parasitaemia was similar to the previous day.

Does this suggest that the child has drug-resistant malaria ?

Question 4

The child was well and aparasitaemic on the third day, and went on to complete a seven day course of oral quinine. At the end of that time a further blood test showed gametocytes "+".

What should be done about the gametocytes present in the blood after treatment ?

CASE STUDY : PATIENT 3

The patient, a 28 year old male from Chandrapur District of Maharashtra was posted in Ladakh for five years. He returned home last month.

One week ago he developed fever. He decided this could not be malaria because he had grown up in a malarious area and believed he was therefore immune. Two days ago he became confused, especially at night. He stayed in bed and was attended by a servant who today called the doctor because the patient was increasingly confused. The last urine he had passed was a small volume of very dark fluid 24 hours ago.

On examination, the patient was a well nourished adult man. He was febrile (rectal temperature 36.5 deg C). He was restless but could make brief appropriate answers to questions, and could localise the site of a painful stimulus. He was jaundiced and his mucous membrane were pale. There was some bleeding from the gums, and there were a few retinal haemorrhages in each eye.

Question 1

(a) What is the differential diagnosis ?

(b) Was the patient right to think he was immune to malaria ? (Justify your answer).

Question 2

The thick blood film shows p. falciparum "++++" and the thin blood film shows that 26% of red cells are parasitized.

(a) What else would you look for in the thin blood film ?

(b) What other tests would you do to investigate the bleeding tendency ?

(c) What treatment is needed for the bleeding ?

Question 3

The patient has passed urine for 24 hours.

What kind of investigations and actions are appropriate ?

Question 4

Fifteen ml of dark brown urine was obtained by catheter. The urine 'stix' tests revealed albumin '++', blood '++++', conjugated bilirubin '++', unrobilinogen '++'. Microscopy of the urine showed no cells and a few casts.

How do you interpret the results of the urine tests ?

Question 5

Acute renal failure is confirmed. Is it possible that the kidneys may recover?

How should quinine therapy be given to this patient with acute renal failure?

SECTION - II

GUIDELINES FOR TRAINERS

MODULAR EXERCISES ON THE DIAGNOSIS AND MANAGEMENT OF SEVERE AND COMPLICATED MALARIA

LEARNING OBJECTIVES

The trainee (physician) will work on three case studies and discuss the answers, so as to have a good knowledge of the :—

* clinical features
* complications
* laboratory aspects
* chemotherapy
* management and monitoring of severe and complicated malaria case

The tutor should satisfy himself that each of the participants has a good grasp of every item, and one of the above objectives in particular being the chemotherapy and management of severe malaria. Inappropriate management of the case may lead to high mortality.

ANSWER BOOK AVAILABLE

Working in not more than three groups the learners should discuss each case and come to consensus on the answers to the questions to be answered.

Not more than 30 minutes should be allowed for each case study.

Each group will then present its findings for ten minutes, which would be followed by a discussion of around thirty minutes. This process is extremely important because of the problem solving approach on which this module is based.

Sufficient time should be allowed to accomplish this properly and the cases should be taken in order of sequence in which they have been shown in the learner's Guide.

As a trainer, you should be fully satisfied that all participants understand the reasoning behind the answers to each question before proceeding to the next case study.

Time should be allotted for a final round table discussion giving the learners full opportunity to clarify any issue that they might not have fully understood. You may wish to stimulate their active participation by way of revision of the subjects. This gives you the opportunity to make a clear synthesis of the subject as a whole, prior to the post-test evaluation.

The suggested answers to the case studies, which should help you in the discussion session following the presentation of the group work, are set out in the following pages. They can be photocopied and used as handouts after the case studies have been completed.

CASE STUDY : PATIENT 1

Question 1

What tests are urgently required ?

Answer : Blood glucose. Pregnant women are susceptible to hypoglycaemia with any stress or infection and they are particularly likely to develop hypoglycaemia (due to hyperinsulinaemia) when treated with quinine. This patient is pregnant and has already received some Quinine, she has altered consciousness. Hypoglycaemia is therefore, a strong possibility and must be checked for urgently.

Haematocritic and parasitic density : Because she is pregnant she may already be anaemic due to iron or Folate deficiency and increased plasma volume. Malaria may rapidly exacerbate anaemia. The risk of developing pulmonary oedema is increased in patients with severe anaemia.

Lumbar puncture, and blood culture if possible : Meningitis may coexist with malaria and could be difficult to identify without examination of the cerebrospinal fluid. Septicaemia may complicate severe malaria. In pregnancy there is increased susceptibility to bacterial infections –e.g. pneumococcal - including septicaemia and meningitis.

Question 2

If the whole-blood glucose is 1.2 mmol/l, what treatment will you give ?

Answer : Intravenous 50% dextrose, 20 ml by intravenous bolus injection. Remember, hypoglycaemia may be recurrent and severe in pregnancy. Monitor the blood glucose level frequently.

Question 3

If the blood film shows *P. falciparum* rings '++++', and the cerebrospinal fluid is normal except for low glucose, then :

(a) What antimalarial drugs will you administer and by which route ?

Answer : Quinine by intravenous infusion. An alternative route for quinine is intramuscular, but the intravenous route is preferable in a centre where a drip can be set up.

(b) Would you prefer an alternative to quinine because the patient is pregnant ?

Answer : Malaria is more dangerous for this patient than quinine; she should receive quinine because it is the best available antimalarial for severe malaria. Studies have shown little oxytocic effect of quinine in these circumstances.

(c) Would you give a loading dose of quinine ?

Answer : A loading dose of quinine should not be given, because the patient has received quinine within the last 24 hours, and a loading dose may therefore lead to dangerously high blood levels of the drug.

(d) What nursing procedures are important during this treatment ?

An important nursing responsibility is the control of the rate of infusion. If quinine is allowed to run too rapidly, hypotension and hypoglycaemia may develop and the patient may become dangerously overloaded with fluid. On the other hand, if the infusion is too slow, inadequate blood levels of the drug may be achieved, and the patient may become dehydrated. Meanwhile, care of the semiconscious patient is essential. As she is restless she must be protected from falling and from pulling out drip lines. Other important nursing procedures are discussed in the following sections.

Question 4

After six hours the patient becomes increasingly restless. The respiratory rate increases to 40/minute. The blood glucose level is normal. Under these conditions, what special observations would you make ?

Answer : Look for evidence of pulmonary oedema, which may complicate falciparum malaria, especially in pregnancy.

Review the urinary volumes passed, the volumes of intravenous fluid (including glucose) given, and the fluid balance. This emphasise the need for precise monitoring and recording of fluid intake and output — another important responsibility of those who nurse the patient are —

Assess the central venous pressure (clinically or, if possible, with the help of a central venous pressure line).

Examine carefully for gallop rhythm, basal crepitations and hepatic enlargement.

Question 5

What other observations are particularly important in this patient ?

Answer : foetal heart rate. Foetal distress is common in malaria, especially if there is high fever. Assisted vaginal delivery or even Caesarian section must be considered if foetal distress is severe.

Question 6

What is the first question that you would ask this patient's relatives ?

Answer : Ask about travel History—when had she visited parts of the country where transmission of malaria occurs? Had she received a blood transfusion in the recent past (an alternative source of malarial infection).

CASE STUDY : PATIENT 2

Question 1

(a) Does the child have cerebral malaria ?

Answer : The fact that the child is now fully conscious suggests that the convulsion was a 'febrile convulsion' rather than a component of cerebral malaria. Convulsions occur in cerebral malaria but they are not followed by rapid recovery of consciousness.

(b) What should you do about the convulsions ?

Answer : Make sure that the risk of a further convulsions is minimised by reducing the child's temperature by (paracetamol, tepid sponging and fan etc).

Question 2

The district hospital is 30 km away; the journey will probably take several hours by bus.

(a) Should the patient be referred to hospital ?

Answer : The decision to refer the patient will depend on facilities available at the health centre. Where drugs and I/v fluids are available. The child also needs to be observed.

(b) What treatment would you give meanwhile ?

Answer : Because the child is persistently vomiting, the first dose of antimalarial drug should be given parentrally. Ideally, this should be by slow intravenous infusion, but since this is not possible in this case, it may be given by intramuscular injection: Inj. quinine (10 mg salt/kg) or, if local parasites are known to be Chloroquine sensitive, Chloroquine (2.5 mg/kg intramuscularly).

Recent studies suggest that a loading dose of quinine (20 mg salt/kg) can safely be given by intramuscular route, as long as the patient has not received quinine or quinidine in the preceding 24 hours or mefloquine in the preceding 3 days.

A reasonable approach is to give quinine 10 mg/kg intramuscularly immediately, then 10 mg/kg intramuscular (the remainder of the loading dose) after 4 hours.

Because of the history of febrile convulsion, make sure that the mother continues to give her child tepid sponging and fanning to reduce the risk of further convulsions.

The child may cease to vomit soon after the injection, especially if the temperature has been successfully lowered. It may then be possible to continue treatment by mouth, without being referred to a larger centre.

Question 3

The child successfully took the second and third dose of quinine by mouth and was brought back to the clinic the next day; there had been little change; the child was still febrile, and the parasitaemia was similar to the previous day.

Does this suggest that the child has drug-resistant malaria ?

Answer : No. Fever commonly persists, and the degree of parasitaemia may remain same for upto 24 hours after the start of treatment, even if the parasite is fully sensitive to the drug being given. However, by 48 hours, the density of parasitaemia should be greatly reduced and the condition of the patient improves.

Question 4

The child was well and aparasitaemic on the third day, and went to complete a seven-day course of oral quinine. At the end of that period a further blood test showed gametocytes '+'.

What should be done about the gametocytes present in the blood even after treatment ?

Answer : Gametocytes are commonly found in the blood for several days or even weeks after successful treatment of falciparum malaria; they do not indicate failure of treatment, and no action is required.

CASE STUDY : PATIENT 3

Question 1

(a) What is the differential diagnosis ?

Answer : Consider all diseases that may lead to encephalopathy with jaundice: i.e fulminating hepatitis, yellow fever, viral fever, relapsing fever, septicaemia, lobar pneumonia (which is commonly accompanied by jaundice), leptospirosis, alcoholism, sickle cell crisis, trypanosomiasis etc.

Nevertheless, under the circumstances if the patient, is not able to pass urine. severe falciparum malaria may be the most likely diagnosis.

Retinal haemorrhages are common in severe malaria, and do not on their own indicate the presence of abnormal bleeding tendency.

(b) Was the patient right to think he was immune to malaria ?

Answer : No, immunity to malaria is partial, and may be almost comp'etely lost if the patient doesn't stay in endemic area for few years.

Question 2

The thick blood film shows *P. falciparum* '+++' and the thin blood film shows that 26% of red cells are parasitised.

(a) What else would you look for in the thin blood film ?

Answer : Platelets. Thrombocytopaenia is common in falciparum malaria but may be particularly severe in this patient who has signs of a bleeding tendency. Severe thrombocytopaenia may be evident on a thin blood film.

(b) What other tests would you carry out to investigate the bleeding tendency ?

Answer : Platelet count and prothrombin time. In addition a bedside test that might be positive in the presence of a low platelet count is Hess's test. If possible it would be interesting to know the plasma fibrinogen and fibrin degradation products (FDPs). If the platelet count and plasma fibrinogen are very low in a patient with spontaneous bleeding the bleeding can be attributed to disseminated intravascular coagulation (DIC). However, if only the thin blood film can be done the scantiness of platelets in the presence of bleeding in a patient with malaria suggests DIC; Hess's test may or may not be positive. The best bedside test for the presence of abnormal bleeding due to DIC is the bleeding time (described in Learner's Guide). In this patient this is likely to be prolonged, since there is abnormal bleeding spontaneously from the gums. A record of bleeding time would be useful in order to monitor progress in response to treatment.

(c) What treatment is needed for the bleeding ?

Answer : Fresh blood transfusion (HIV negative). Alternatively fresh frozen plasma (this replaces fibrinogen but not platelets) and platelet-rich plasma. Vitamin K is not helpful since the bleeding is not due to vitamin K deficiency. Since this patient may need blood-transfusion for malarial anaemia also, it would be wise to prepare urgently as many safe units of whole fresh blood as possible.

Question 3

The patient has not passed urine for 24 hours. What investigations and actions are appropriate ?

Answer : Palpate the abdomen to see if the bladder is distended. Try to help the patient to pass urine. If he cannot, catheterize with full sterile procedure, in order to record urine volume carefully. Test the urine by routine method and if possible for sodium concentration and specific gravity also. The management is like that of any other patient suspected to be having acute tubular necrosis-i.e. correct any under-hydration by careful saline infusion (urine specific gravity $\geq$1.015 and sodium $\leq$20 mmol/l suggests dehydration), and if

necessary, use drugs such as furosemide and dopamine for proper flow of urine. Measure blood urea, serum, creatinine and serum electrolytes if possible; and electrocardiograph helps to demonstrate hyperkalaemia. If acute tubular necrosis gets established, intensive care is required, with peritoneal dialysis or haemodialysis.

Question 4

15 ml of dark brown urine was obtained by catheter. The urine stix tests revealed albumin '++' microscopy of the urine showed no cells and few casts.

How do you interpret the results of the urine test ?

Answer : The presence of 'blood' in the urine (i.e. haemoglobin) in the absence of red blood cells indicates that there is free haemoglobin in the urine, as a result of intravascular haemolysis, a complication of severe falciparum malaria. Billirubinimia indicates that there is some increase in the conjugated hyperbillirubinaemia, as in haemolysis. Proteinuria is usual in the presence of acute tubular necrosis, which is the commonest form of renal failure in falciparum malaria.

Question 5

Acute renal failure is confirmed. Is it possible that the kidneys may recover ?

Answer : Yes, in acute tubular necrosis, recovery commonly takes place within a period of few weeks. It is therefore important to keep the patient alive, if possible, by dialysis (usually peritoneal dialysis) - because full recovery is then likely, without the need for continued long-term dialysis.

How should quinine therapy be given to this patient with acute renal failure ?

Answer : If acute renal failure is confirmed, the first dose of quinine should be the same as in any other patient with severe malaria, but if acute renal failure has established, the dose should be reduced by 50% from the third day onwards.

Note : Peritoneal dialysis can be life-saving and the results are achieved without the use of costly equipment. However, it requires experience and competence. Guidelines for indications and methods of peritoneal dialysis are available and should be taught and demonstrated to hospital staff who may be responsible for management of patients with severe malaria. Fortunately, acute renal failure is very rare in African children with severe malaria.

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